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BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH

DIVISION OF RESEARCH SERVICES

NATIONAL INSTITUTES OF HEALTH

ANNUAL REPORT FY 1982

Dr. Murray Eden, Chief

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10001-14 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Pharmacokinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. L. Dedrick	Chief	ChES BEIB DRS
	J. M. Collins	Chemical Engineer	BEIB DRS
OTHERS:	D. S. Zaharko	Pharmacologist	LCHPH NCI
	F. King	Associate Professor	Howard University
	R. J. Lutz	Chemical Engineer	BEIB DRS
	P. M. Bungay	Chemical Engineer	BEIB DRS
	H. B. Matthews	Pharmacologist	NTP NIEHS
	C. E. Myers	Chief	CPB NCI
	M. F. Flessner	Chemical Engineer	U. Md./ NIH
	N. Bachur	Chief	LCB NCI
	P. Poplack	Pediatrician	POB NCI
	B. Smith	Neurosurgeon	SNB NINCDS
	S. Zimm	Oncologist	POB NCI

COOPERATING UNITS (if any)
LCHPH-NCI; LCB-NCI; SNB-NINCDS; CRS Program NIAMDD; M-NCI; NTP-NIEHS; CPB-NCI; POB-NCI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Pharmacokinetic models are developed for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man. They provide a plausible set of equations that can be used to extrapolate data from animals to man and thereby improve chemotherapy, and risk assessment.

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Objectives: Improve and extend mathematical models for the distribution and disposition of drugs, environmental contaminants, and endogenous metabolites in animals and man to:

(1) Account for species differences in drug distribution.

(2) Provide a rational basis for extrapolating toxicity from animals to man.

(3) In conjunction with pharmacodynamics, provide a basis for optimizing cancer chemotherapy and chronic hemodialysis.

(4) Enable rational transfer of in vitro thermodynamic and kinetic data to in vivo cases.

(5) Predict effective dose schedules of anticancer drugs in individual patients with particular emphasis on intraperitoneal drug administration and also drug delivery to the brain.

Methods Employed: Mathematical models are developed from physicochemical, physiological, and anatomical information and the principles of chemical reaction engineering. Resulting sets of ordinary of partial differential equations are solved analytically or numerically and compared with experimental data. Uncertainties are clarified by additional experiments and model modification.

Major Findings: (1) Limited physiologic model has been developed to describe the time course of 2,3,7,8 - tetrachlorodibenzofuran (TCDF) in the blood and tissue of rats, mice, and monkeys. The liver shows the greatest tendency to concentrate the material with tissue-to-blood distribution coefficients ranging from 30 in the monkey to 130 in the mouse. TCDF is also concentrated in the fat with tissue-to-blood distribution coefficients between 25-40 in all species. TCDF is eliminated by metabolism followed by excretion primarily to the feces. Urinary excretion is a minor route of elimination in all species. Metabolism is modeled as a linear process occuring in the liver. Intrinsic rates of metabolism range from 0.45 ml/min/kg in the monkey to 2.8 ml/min/kg in one species of mice. Fecal excretion of TDCF derived radioactivity can be simulated with a stirred-tanks-in-series model which receives input of metabolite in the bile.
(2) A flow-limited physiologic mathematical model has been developed to describe the time course of 2'deoxycoformycin (2'dCF) concentrations in the plasma and tissues of mice following iv and ip doses. Urinary excretion is modeled as a linear process involving filtration and secretion, since kidney clearance exceeded estimated glomerular filtration rate. Intracellular binding is described as the sum of linear nonspecific binding plus strong saturable binding to adenosine deaminase. Pharmacokinetic parameters are determined by a sequential optimization scheme in which each tissue is studied by means of a hybrid model. The model has been used to predict pharmacokinetic behavior of 2'dCF in both normal and leukemic mice, and model simulations are compared with published data. (3) A distributed mathematical model is being developed to describe the transport of cisplatin from the peritoneal cavity through peritoneal tissue and into plasma. The model includes diffusion through peritoneal tissue, transport across blood capillaries, and the reaction of free cisplatin to form aquation products. The aquation products are assumed to be instantaneously and

irreversibly bound to peritoneal tissue. Blood capillaries are assumed to be uniformly distributed throughout the tissue. The model simulations of the bound platinum concentration profile will be compared to experimental data from experiments which are in progress. (4) A distributed model has been developed to describe diffusive peritoneal transport of solutes. The model permits explicit prediction of peritoneal permeabilities from observations on the microcirculation and intratissue diffusivity. It has been compared with existing membrane theory and is consistent with a large body of information on variation of transport parameters with molecular weight of the solute and body weight of the animal. (5) The rate of transfer into and out of CSF has been studied in both monkeys and man for 5 anticancer drugs (6MP, 5FU, AZQ, AraC, and interferon). In conjunction with these experiments, a distributed model for drug delivery to CSF is being developed. (6) Pharmacokinetics of the investigational drug, AZQ, have been completed in mice, dogs, and man. Tissue distribution was studied in mice, intracarotid artery administration in dogs, and CSF penetration in clinical studies. (7) We are continuing pharmacokinetic support of intraperitoneal drug administration. Clincal studies were completed with the radiosensitizers misonidazole and desmethylmisonidazole while 5FU studies are continuing.
(8) Toxicity extrapolation from mice to man is being investigated in a project whose aim is to improve the efficiency of dose escalation in Phase I trials. Relationships between pharmacokinetics and toxicity are being evaluated both retrospectively and prospectively. (9) Adriamycin i.v. pharmacokinetic studies in man have been completed, including quantitation of adriamycin's concentration-time course and binding of both compounds by plasma proteins. (10) Completed studies of the use of a test dose of methotrexate to provide for individualized dose selection in high-risk patients. (11) Study of pulmonary clearance of BUDR in humans is ongoing.

Significance: Drugs and other chemicals are tested for effect in animals, with the aim of extrapolating results to man. At issue are both the risk associated with environmental contaminants and optimization of therapy.

Proposed Course: Continued pharmacokinetic modeling with consideration of pharmacodynamic and cytokinetic events and drug interactions. Continued clinical emphasis through support of intraperitoneal procedures and other measures to overcome drug resistance. Increased emphasis on research designed to investigate distribution and metabolism of environmental contaminants and on methods for incorporating pharmacokinetics in models of risk assessment. Investigation of use in *in vitro* assays of chemical metabolism in conjunction with pharmacokinetic models for quantitative prediction of metabolism *in vivo*.

Publications

J. M. Collins. "Inert gas exchange rates of subcutaneous and intraperitoneal gas pockets in piglets," Resp. Physiol. 46:391-404 (1981).

M. E. McManus, Monks, A., Collins, J.M., White, R., and Strong, J.M. "Nonlinear pharmacokinetics of misonidazole and desmethylmisonidazole in the isolated perfused rat liver", J. Pharmacol. Exp. Ther. 219:669-674 (1981).

C. L. Litterst, J. M. Collins, M. C. Lowe, et al. "Local and systemic toxicity resulting from large volume ip administration of doxorubicin in the rat," Cancer Treat. Rep. 66:157-161 (1982).

J. M. Collins and R. L. Dedrick. "Contribution of the lung to total body clearance: linear and nonlinear effects:, J. Pharm Sci. 71:66-70 (1982).

J. M. Collins and R. L. Dedrick. "Pharmacokinetics of Anticancer Drugs," pp. 77-99 in "Pharmacologic Principles of Cancer Treatment" edited by B. A. Chabner. W. B. Saunders, Philadelphia, 1982.

J. M. Collins, R. L. Dedrick, M. F. Flessner, and A. M. Guarino. "Concentration-dependent disappearance of fluorouracil from peritoneal fluid in the rat: Experimental observations and distributed modeling", J. Pharm. Sci., in press.

N. R. Bachur, J. M. Collins, J. A. Kelley, et. al. "Diaziquone, 2, 5-diaziridinyl-3,6-biscarboethozyamino-1,4-benzoquinone, plasma and cerebrospinal fluid kinetics", Clin. Pharmacol. Ther. 31:650-655, 1982.

R. L. Dedrick, M. F. Flessner, J. M. Collins, J. S. SchultZ. "Is the peritoneum a membrane?:, ASAIO Journal, in press.

R. J: Lutz, "Introduction in Receptor-Binding Radiotracers", Vol. II, W. C. Eckelman and L. G. Colombetti (eds.), CRC Press, Boca Raton, Florida, 1982, pp. 3-6.

King, F.G. and Dedrick, R.L.: Physiologic Model for the Pharmacokinetics of 2'deoxycoformycin in Normal and Leukemic Mice. J. Pharmacokin. and Biopharm. 9, 519-534, 1981.

Bungay, P.M., Dedrick, R.L., and Matthews, H.B.: Enteric Transport of Parent chlordecone (Kepone^{R}) in the Rat. J. Pharmacokin. Biopharm., 9, 309-341, 1981.

Dedrick, R.L.: An Engineer's Perspective on Environmental Toxicology. Paper No. 108a, 74th Annual AIChE Meeting., New Orleans, 1981.

Dedrick, R.L.: Interspecies Dose-Response for Radiogenic Bone Cancer. Science, 214, 207, 1981.

Bungay, P.M., Dedrick, R.L., Matthews, H.B.: Physiological Model of Enteric Transport, Proc. 12th Conf. Environ. Toxicol., Dayton, Ohio, 287-198, 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10002-17 BEI

PERIOD COVERED
October 1, 1981 to September 1981

TITLE OF PROJECT (80 characters or less)
Implant Device Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.W. Boretos	Physical Scientist	BEIB, DRS
OTHER:	W.S. Pierce	Professor	Penn State University
	J. Doppman	Radiologist	CR CC
	E. Glatstein	Chief	RO NCI
	H. Gabelnick	Chemical Engineer	NICHD

COOPERATING UNITS (if any)
CR-CC; Pennsylvania State University, RO, NCI, NICHD

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.7	OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of the project is to elucidate the interaction of biomaterials used for specific implants with the physiological environment and to explore specially prepared biomaterials and design features with respect to their suitability and performance in a variety of contexts. After removal from the host organism, implants will be examined for lipid absorption, changes in surface-free energy, and alteration of physical properties. Observations should include scanning electron microscopy, infrared spectroscopy, contact angle measurements, and energy dispersive X-ray analysis. Physical measurements will be made of tensile properties, flexural-fatigue resistance, electrical properties, hardness, density, coefficient of static and kinetic friction, hydrophilicity, and other surface and bulk properties.

Objectives: Elucidate the interaction of polymers, metals, and ceramics used for specific implants with the physiological environment; explore specially prepared polymers and design features with respect to their suitability and performance in a variety of contexts.

Methods Employed: Basic composition of biomaterials is carefully controlled, and modifications are employed to enhance acceptability by the living system. After removal, implants are examined for lipid absorption, protein and/or calcium deposition, changes in surface-free energy, and alteration of physical properties. Observation techniques include SEM, infrared spectroscopy, contact angle measurements, energy dispersive X-ray analysis, and atomic absorption spectroscopy. Flow characteristics and pressure gradients across heart valve implants are studied in vitro in a test apparatus. Electronic implants are examined periodically in vivo for changes in threshold levels, corrosion, and tissue activity. In vitro studies of the aforementioned are designed to accelerate fatigue testing and methods of improvement through heat treatment of the metal components undergoing stress. Surfaces of catheters are modified using surface treatments of grafted polymers and copolymers to reduce drag through the blood vessels. These catheters are tested for burst strength, stiffness, tensile strength, and density. The basic composition is modified through compounding. Embolizing agents consisting of composites of polymers, ceramics, and metals are being devised for delivery through the catheter systems so as to block arteries and vessels in the treatment of lesions such as aneurysms and arteriovenous malformations.

Major Findings: Segmented polyurethane undergoes small initial changes in tensile properties when stored dry for 13½ years and appears not to undergo appreciable changes on further aging. Storage in non-sterile water leads to deterioration in tensile properties.

Significance: Physiologically compatible polymers with enduring strength are needed for such applications as heart valves, heart-assist devices, vascular implants, indwelling catheters, and subcutaneous uses.

Proposed Course: Extend experimental studies to further characterize the surface and bulk properties of biomaterials and, more specifically, determine their interactions with blood and subcutaneous tissue to facilitate development of better surgical implants.

Publications

Boretos, J.W.: Hydrogel Coating of Polyurethane for Increased Surface Lubricity. Transactions of the 7th Annual Meeting of the Society for Biomaterials, Troy, N.Y., May 28-31, 1982, p. 71.

Boretos, J.W.: Long Term In Vitro Stability of Segmented Polyurethane. Transactions of the 8th Annual Meeting of the Society for Biomaterials, Orlando, Florida, April 24-27, 1982, p. 25.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10015-07 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of Miniature Catheter for Clinical Use

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. Shook	Biomedical Engineer	BEIB DRS
OTHER:	S.R. Goldstein	Chief	MES BEIB DRS
	J.L. Doppman	Chief	DR CC

COOPERATING UNITS (if any)
DR-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.6	0.9	0.7

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A miniature toposcopic catheter attached to the end of a conventional catheter has been developed for insertion in tortuous blood vessels as small as 1 mm in diameter and up to 30 cm long. The miniature topo element has been fabricated in a 3F size, attached to a 5F conventional catheter, and in a 5F size, attached to a 7F catheter. Catheter tests in anesthetized dogs have been highly successful - the catheter is able to penetrate parts of the vascular system which are inaccessible by existing techniques. The apparatus has been redesigned to provide the reliability and convenience required for clinical use. The catheter will enable the delivery of embolizing agents or other therapeutic substances so that some procedures previously requiring surgery can be performed instead with catheters. Techniques of steering the catheter are being developed and efforts are in progress to allow aspiration of fluid from remote areas.

Objectives: Develop techniques and devices for inserting a miniature catheter into small tortuous vessels and steering it into selected branches.

Develop techniques and devices for delivering therapeutic materials into the catheterized vessel for clinical usage and to aspirate fluids from these locations.

Major Findings: Toposcopic catheters of 3F and 5F sizes have been successfully tested in dogs for contrast infusion capabilities and extravascular contrast staining in major organ and muscle systems. Successful in vitro studies of bolus infusion of cyanoacrylate adhesives show promise for canine testing and subsequent clinical use. Also, major design modifications have produced a more precise, compact, and conveniently used device.

Significance: Surgeons and radiologists have long sought techniques for catheterizing small diameter vessels separated from larger, easily catheterized vessels by long, narrow passages with numerous bifurcations. The capability would permit selective treatment of tumors, aneurysms, arterio-venous malformations, and other lesions with minimal danger to normal tissues. Delivery of embolizing agents and materials to stain tissue, as well as aspiration of fluid, are contemplated.

Proposed Course: Complete design modifications required for clinical use. Test newly developed applications for the device in animal studies in preparation for clinical use. Refine development efforts to permit steering the toposcopic catheter through branched and bifarcated vasculature, and adapt resulting changes to existing system. Develop related devices and explore additional use for the catheter.

Publications

Goldstein, S.R., Shook, D.R., Peterson, J., Markle, D., Doppman, J.L., Patterson, R.: The Toposcopic Catheter and the Fiber Optic pH Probe -- Two Medical Instruments of Potential Use to Gastroenterologists. Digestive Diseases and Science. (In Press)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10027-06 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Development of Whole-Body Hyperthermia Instrumentation and Control System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. H. Schuette	Chief	ACES BEIB DRS
OTHER:	J. Bull	Senior Investigator	MC DCT NCI
	D. Lees	Staff Anesthesia	CC NIH
	R. Corsey	Electronic Engineer	BEIB DRS
	H. Tipton	Mechanical Engineer	BEIB DRS
	R. Smith	Nurse	MC DCT NCI

COOPERATING UNITS (if any)
MC-DCT-NCI; CC-NIH; MS-DCT-NIH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Whole body hyperthermia is being studied at NIH as a possible means of treatment for cancer. This project includes development of an instrumentation and control system based on utilization of a Tektronix 31 programmable calculator, digital plotter, and interface for data acquisition. The esophageal temperature of the patient is regulated to $0.1^{\circ}C$ accuracy by feedback control of the temperature of water circulating in a set of hyperthermia blankets. The NIH phase of this project was completed August 1980, however additional publications have been made.

Methods Employed: A Tektronix 31 programmable calculator is being used to acquire, record, and process data as well as to control water temperature of a set of hyperthermia blankets. The temperature of the water pumped through the blankets together with esophageal and rectal temperatures of the patient are processed by the calculator, which then develops temperature commands for the water temperature mixing valve. The mixing valve adds hot or cold water to the flow stream returning from the blankets as directed by the Tektronix digital interface unit so that heart rate, blood pressure, and temperature data could be processed by the system. The multiplexer module also provides commands from the calculator to the water mixing valve motor. Automatic cool-downs are programmed into the calculator in response to various out-of-limit conditions. The calculator functions in an interactive mode for entry of operational instructions.

Major Findings: The major finding from the use of the equipment is that it is possible to take the whole-body core temperature of patients to 42.0 ± 0.1°C for four hours on a biweekly basis without major difficulty. The finding suggests that hyperthermia treatment for cancer is practical. Currently, the system is being employed in conjunction with chemotherapy at the Herman Hospital, Houston, Texas.

Publications

Whang-Peng, J., Lees, D.E., Schuette, W.H., et al.: "Erythrocyte Osmotic Fragility in Patients Receiving Hyperthermia With and Without Chemotherapy", Cancer Treatment Reports, Vol. 65, No. 11-12, Nov., Dec. 1981.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10034-05 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Three-Dimensional Histological Reconstruction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. B. Leighton	Mechanical Engineering	BEIB DRS
OTHER:	A.M. Kuzirian	Neuroanatomist	LB NINCDS

COOPERATING UNITS (if any)
LB NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.5	.45	.05

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ■ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A semi-automatic system for acquisition of three-dimensional structural information about histological material is being developed. The system should have significant speed and reliability advantages over present techniques using serial sections, although resolution may be limited. In brief, an embedded tissue block will be fixed relative to a scanning electron microscope imaging system, the surface of the block will be imaged and stored, and successive slices will be removed by a built-in microtome. Handling and registration of thin sections will thus be eliminated. Human and computer pattern recognition will transform the resulting set of images into a three-dimensional reconstruction.

Objectives: (1) To facilitate making schematic diagrams of neural networks. (2) To facilitate developmental studies of small organs and organisms. (3) To do three-dimensional reconstruction of biological structures.

Methods Employed: A miniature microtome has been built to function within the vacuum chamber of a scanning electron microscope. The microtome has cut sections as thin as 0.5 microns. Glycol Methacrylate has been tried as an embedding medium, and oxygen plasma as an etching means.

Major Findings: Satisfactory images of monkey retina have been obtained, using the glycol methacrylate and oxygen plasma etching.

Significance: Neuroanatomists may be able to trace significant neural nets with sufficient ease to allow a statistically significant number of samples. Other biological studies may be materially aided.

Proposed Course: The system will be integrated with an existing computer for image processing for semi-automatic three-dimensional reconstructions. Further improved embedding media will be tested to give a better etching effect and increased resolution. Additional types of tissue, such as Hermissenda Crassicornis, will be tried. Feedback will be used to reduce the section thickness to 0.1 micron.

Publications

Leighton, S.B.: "A Miniature Microtome for Use Inside Scanning Electron Microscope", 1981 Advances in Bioengineering, ASME, NY.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10039-05 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Biophysical Instrumentation and Methodology

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHER:	T.R. Clem	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH

SECTION
Microanalysis

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The project is designed to develop new instrumentation and methodology or improve existing instrumentation and methodology for characterization of biological macromolecules. Analytical ultracentrifugation and the techniques ancillary to it are the major areas of interest.

Objectives: To develop data acquisition systems for analytical ultracentrifuges and for ancillary equipment such as plate or film readers and densimeters, to develop appropriate software to use with the acquisition systems, and to study means of utilizing MLAB more effectively for the analysis of ultracentrifuge data by mathematical modeling techniques.

Methods Employed: A microprocessor controlled instrument has been developed for the acquisition and temporary storage of data from the optical comparator used for the measurement of photographically recorded data from the analytical ultracentrifuge. This instrument is coupled to a Columbia Data Systems desk-top minicomputer which provides (1) permanent storage of data on mini-floppy discs; (2) preprocessing of the data; (3) graphic display of the data and editing capabilities if needed; and (4) communication with the DEC-10 computer permitting transfer of the data to the DEC-10, control of data analysis using the MLAB system on the DEC-10, and the transfer of the results of these analyses back to the laboratory. Software is being developed for optimizing the data acquisition for different modes of acquisition and for data editing prior to transmission to the DEC-10. Work is also under way for using this mini-computer with a data acquisition system for directly obtaining data from the absorption scanning system of the analytical ultracentrifuge, and then fulfilling the same functions as for the comparator data acquisition system.

Major Findings: The system for acquiring data from photographically recorded ultracentrifuge data has proved to have significant advantages in speed and accuracy. Programs are being developed for the reduction of data acquired in different acquisition modes and for editing it prior to transmission to the DEC-10. A program has also been developed for the calculation of partial specific volumes of proteins from their amino acid compositions. Improved methods for the analysis of interacting systems by mathematical modeling utilizing MLAB on the DEC-10 computer have been developed.

Significance: Since data acquisition has been the limiting factor in terms of the qualitative and quantitative aspects of ultracentrifugal research, it is expected that the continuing development of these data acquisition systems described above will significantly facilitate such research. The improved methods of data analysis by mathematical modeling also contribute to the quality and the time and cost effectiveness of this research.

Proposed Course: Continue the developments outlined above.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10040-05 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Physical Chemistry of Biological Macromolecules

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	M.S. Lewis	Research Chemist	BEIB DRS
OTHERS:	S.I. Chung	Research Chemist	LB NIDR
	J.A. Gladner	Research Chemist	LCB NIAMDD
	L. Leive	Research Chemist	LBP NIAMD
	L. Levenbook	Research Chemist	LPB NIAMDD
	A.P. Minton	Research Chemist	LCB NIAMDD
	J. C. Osborne	Research Chemist	MD NHLBI
	M. Rosenberg	Section Chief	LB NCI
	B. Wiggert	Rsearch Chemist	LVB NEI
	H. Yeh	Research Chemist	LC NIAMDD

COOPERATING UNITS (if any)

LB-NIDR, LCB-NIAMDD, LBP-NIAMDD, LPB-NIAMDD, LCB-NIAMDD, MD-NHLBI, LB-NCI, LVB-NEI, LC-NIAMDD

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Microanalysis

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.8	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the physical properties of a wide variety of biological macromolecules with the goal of correlating these properties to the structure and function of the macromolecules. The emphasis is on molecular size and shape, the thermodynamics of molecular interactions and on molecular weight distribution. Analytical ultracentrifugation and mathematical modeling are the principal research techniques used.

Objectives: (1) To study the self-association of hemoglobin and myoglobin at physiological concentrations; (2) To study the molecular weight distribution of an acetylated lipopolysaccharide from the cell walls of E. coli; (3) To study the thermodynamics of the self-association of the c-II protein produced by E. coli with a cloned in lambda-phage protein producing region; (4) To study the thermodynamics of the association of various forms of plasminogen with fibrinogen; (5) To study the thermodynamics of the self-association of 7 S retinol binding protein; (6) To study the effects of surface activity on solute distribution in the ultracentrifuge; (7) To study the thermodynamics of the self-association of the insect protein calliphorin; (8) To study the thermodynamics of the self-association of the A-2 phospholipases from the venoms of certain snakes.

Methods Employed: The various macromolecules have been isolated and purified from appropriate sources by conventional methods or have been prepared synthetically. The molecular weights have been determined by analytical ultracentrifugation and the resultant data has been analyzed by mathematical modeling techniques using the MLAB system on the DEC-10 computer. Mathematical modeling techniques have also been used for studies of molecular weight distribution and for studies on fitting ultracentrifuge data. Partial specific volumes have been determined by densimetric techniques.

Major Findings

Myoglobin Self-Association: The ultracentrifugal behavior of myoglobin and hemoglobin at very high concentrations has been studied in order to determine whether or not myoglobin undergoes any associative reaction at physiological concentrations. The problem of the possible association of myoglobin being masked by the very marked thermodynamic non-ideality at high concentrations was treated by studying the ratios of the apparent molecular weights of myoglobin and hemoglobin as functions of concentration, since both are heme proteins with very similar molecular weights for the monomer and the associative behavior of hemoglobin has been well studied. The data clearly demonstrate that myoglobin associates as least as far as the dimer stage and that further association might be possible. The results of this study have been published.

E. Coli Lipopolysaccharide: The studies on the molecular weight distribution of the acetylated lipopolysaccharide of the cell walls of E. coli have had some unusual aspects. This material has been soluble only in such solvents as dichloromethane, trichloromethane, chlorobromoethane, and dibromomethane. The different densities of these solvents has made it possible to obtain the partial specific volume and the mean molecular weight of the polymer from the same sets of data. A mean weight average molecular weight of 718,000 was obtained, and a ratio of 1.36 for the weight average molecular weight to the number average molecular weight indicated a very marked degree of polydispersity. The results of this study have been published.

C-II Protein: This protein has been obtained form a system where a lambda-phage protein coding region has been cloned into a plasmid for overproducing proteins in E. Coli. The total amino acid sequence of this protein is known. It has been found to undergo a monomer-dimer-tetramer reversible self association, with the association to form dimer appearing as a relatively weak type of hydrophobic bonding, and the association to from tetramer appearing as a relatively strong type of hydrophobic bonding. This protein is a positive activator of transcription. The results of this study have been published.

Plasminogen-Fibrinogen Interaction: The association of fibrinogen with glu-plasminogen, the native form, and with lys-plasminogen, the modified form produced by the removal of a 4000 molecular weight peptide by either plasmin or urokinase, has been studied by ultracentrifugal analysis. While the changes of free energy of association of the two forms of plasminogen with fibrinogen differ to some extent, the mechanism for the association of either form of plasminogen with fibrinogen appears to be the same. There appear to be four binding sites for plasminogen per fibrinogen molecule. The binding of the first plasminogen appears to be a relatively weak hydrophobic interaction, while the binding of the remaining three plasminogen molecules appears to involve relatively strong hydrophobic interactions. This implies a very marked degree of cooperativity of binding and suggests significant configurational changes when the interactions take place. A manuscript describing this work is being prepared.

Retinol Binding Protein: Studies on the self-association of 7 S retinol binding protein show that it undergoes a monomer-dimer-tetramer type of self association with the free energy change for the dimer-tetramer association greater in magnitude than the free energy change for the monomer-dimer association. Both free energy changes are characteristic of hydrophobic bonding. This work has been presented at a meeting and a manuscript describing it is being prepared.

Lipoprotein Surface Activitiy: Studies on plasma apolipoproteins show that they exhibit a significant level of surface activity and that this surface activity might result in significant alterations of the concentration distribution in the ultracentrifuge cell. A thermodynamic theory for the effect of surface activity on concentration distribution has been derived and mathematical modeling shows that while the effect is small, it might be of some significance under certain experimental conditions. The application of theory to experimental data is now in progress.

Insect Proteins: Calliphorin is the major soluble protein found in the blowfly, calliphor vicina, during its larval and pupal stages, comprising up to 50% of the protein in this category. It reaches this high level early in the larval stage and remains there for seven of the nine days of pupation, but without metabolic turnover, and then diminishes rapidly and has essentially disappeared by the end of the second day of adulthood. The studies on the self-associative properties of this protein show that the protein is a hexamer at pH's below 7.4, and then undergoes reversible pH dependent dissociation toward monomer with a molecular weight of 78,000 at higher pH's.

Snake Venom Phospholipases: A-2 Phospholipases have been obtained from the venoms of the elapidae naja naja etra, naja nigra collis, and hemachatus haemachatus. These have been found to have monomer molecular weights of 13,000-14,000 and to undergo reversible self-association to form dimers. These studies are part of an overall effort to correlate structure and function of these phospholipases.

Significance: The studies of myoglobin at high concentrations are relevant to the behavior of the oxygen-binding heme proteins at physiological concentrations. The studies on the lipopolysaccharide are relevant to a study of the properties of bacterial cell walls. The studies on the self-association of the C-II protein are particularly interesting because they represent the first step in a series of studies where a correlation may be made between primary structure of a protein and its self-associative behavior. The sequences of some 400 mutant forms of the DNA synthesizing this protein are known, offering a unique opportunity to attempt to make this correlation. The studies on the plasinogen-fibrinogen interaction are relevant to the very significant roles that these proteins play in blood clotting. The studies on retinol binding protein are relevant to the role that this protein plays in the visual process. The studies of the surface properties of the plasma apolipoproteins are relevant to the role of these proteins involved in interaction with plasma lipids. The studies on calliphorin deal with properties that are related to the structure of a protein that undergoes unusual metabolic changes during the process of metamorphosis of an insect and where knowledge of the factors controlling this might be of use in controlling insect growth and metamorphosis in general. The studies on the sanke venom phospholipases are intended to give insight into one aspect of species differences of a particular enzyme.

Proposed Course: New studies on hemoglobin and myoglobin will be undertaken when the ultracentrifuge data acquisition system has been completed and the improved precision possible will make such studies more productive. Studies on some of the mutant forms of the c-II protein are in progress and more are planned. Extensive studies on the plasminogen-fibrinogen interaction are in progress. Studies on lipoprotein surface activity, insect proteins and snake venom phospholipases will be continued.

Publications

Minton, A.P. and Lewis, M.S. "Self-Association in Highly Concentrated Solutions of Myoglobin, A Novel Analysis of Sedimentation Equilibrium of Highly Monideal Solutions", Biophysical Chemistry 14:317-324, 1981.

Ho, Y-S., Lewis, M.S. and Rosenbert, M. "Purification and Proerties of a Transcriptional Activator: The C-II Protein of Phage", Journal of Biological Chemistry, 257:9128-9134, 1982.

Goldman, R.C., WHite, D., Orskov, F., Orskov, I., Rick, P.D., Lewis, M.S., Bhattacharjee, A.K. and Leive, L. "A Surface Polysaccharaide of Esherichia Coli 0111 Contains O-Antigen and Inhibits Agglutination of Cells by O-Antiserum", Journal of Bacteriology, 151:1210-1221, (1982).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 RS 10043-05 BEI

PERIOD COVERED October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Fiber Optic Probes/Oxygen

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J.I. Peterson	Chemist	BEIB, DRS

COOPERATING UNITS (if any)
H-IR-MH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .75	PROFESSIONAL: .75	OTHER: 0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The development of an implantable fiber-optic pO_2 probe for clinical and physiological measurements has continued through this year. The fiber-optic pH probe we developed earlier is a general model for the current design. The pO_2 probe is an optical device for measuring oxygen tension in the body, based on oxygen's effect of decreasing the fluorescence of certain dyes.

PHS-6040
(Rev. 2-81)

Objectives: Develop an oxygen sensor for physiological implantation in the blood stream and tissues to be used in studies of oxygen transport during exercise, and clinical pO_2 measurements.

Methods Employed: A fiber optic measurement of dye-indicator response to oxygen by fluorescence quenching.

Significance: pO_2 measurements are fundamental to understanding and control of oxygen transport in research and clinical investigations. Measurements on withdrawn blood samples lack convenience, reliability, and relevance to many situations of interest. Indirect estimation of pO_2 using spectrophotometric measurements of hemoglobin oxygenation and the concentration-pressure transfer function (blood oxygen saturation curve) is subject to too many uncertain variables. Development of a fiber optic pO_2 probe would represent a significant advance in the ability to directly and continuously measure blood and tissue oxygen. A satisfactory electrode for general use has never been developed, and the fiber optic approach offers some distinct advantages in small size, flexibility, and safety.

Major Findings and Proposed Course: Previous work involved solving the problems of finding a suitable dyes, a suitable support for the dye, and an oxygen permeable containment system, along with evaluation of the performance of probe construction methods. Suitable instrumentation was developed for testing probes and evaluating their performance.

The current year has been devoted to improving probe design and construction, which has resulted in the ability to make probes which perform consistently and reliably. Following this, evaluation of the probe with in-vitro and animal tests is being done. The probe seems to be satisfactory, and it is expected that next year's effort on this project will be related to practical research application, with some adaption or modification of the probe possibly being needed.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10050-04 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Positron Emission Tomography Scanner

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	G. DiChiro	Section Chief	SN NINCDS
OTHER:	R.A. Brooks	Senior Staff Fellow	SN NINCDS
	V.J. Sank	Research Physicist	SN NINCDS
	W.S. Friauf	Electronics Engineer	EEES BEIB DRS
	S.B. Leighton	Mechanical Engineer	MES BEIB DRS
	H.E. Cascio	Electronics Engineer	EEES BEIB DRS
	G.L. Hemphill	Electronics Technician	EEES BEIB DRS

COOPERATING UNITS (if any)
SN NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
EEES, MES

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 3.5	PROFESSIONAL: 3	OTHER: .5

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☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☒ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A custom PET scanner is being developed to provide compromises between resolution, sensitivity, count rate capability, and cost that are optimal for human neurological research requirements at NIH.

Objectives: Design and build a PET scanner with higher resolution and sensitivity than other custom or commercial machines.

Methods Employed: Novel features of the Neuro-PET design include: a large number of BGO detectors tightly packed in a smaller ring than other designs; individual single rate counters for each detector; high accuracy timing to allow use of short coincidence resolving times; accurate energy analysis to facilitate statistical compensation for scattering artifact; and a scanning program that provides optimal spatial sampling.

Major Findings: During the past year the system has been put into operation with 3 slices of its ultimate 7 slice capability. Studies on phantoms indicate that all original performance objectives have been realized. Clinical usage with several dozen patients indicates that the high resolution and sensitivity are of great value for both research and diagnostic purposes.

Significance: The improved capabilities of the Neuro-PET scanner will allow the full potential of PET scanning to be explored effectively. The combination of high sensitivity and high resolution is currently being exploited to enable flow studies to be carried out. Extension of operations to the full 7 slices, and further developments in image processing will allow further applications.

Publications

Brooks, R.A., Sank, V.J., DiChiro, G., Friauf, W.S., and Leighton, S.B.: "Design of a High Resolution Positron Emission Tomograph: The Neuro-PET. Journal of Computer Assisted Tomography 4(1): 5-13, February, 1980.

Brooks, R.A., Sank, V.J., Friauf, W.S., Leighton, S.B., Cascio, H.E., and DiChiro, G.: Design Considerations for Positron Emission Tomography. IEEE Transactions Biomed. Eng. Vol BME-28, No. 2, Feb. 1981, pp. 158-177.

Patents: Four applications are in process.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10053-04 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Membrane Based Sampling Systems for in In Vivo and In Vitro Kinetic Studies

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P.M. Bungay	Chemical Engineer	ChES BEIB DRS
OTHERS:	J. P. Froehlich	Senior Investigator	GRC NIA
	R.L. Berger	Section Chief	LTD NHLBI
	J. Fenstermacher	Section Chief	LCHPH DCT
	R.L. Dedrick	Section Chief	ChES BEIB DRS

COOPERATING UNITS (if any).

Gerontology Research Center-NIA; Laboratory of Technical Development-NHLBI; Laboratory of Chemical Pharmacology-DCT.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.0	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Synthetic membranes are being utilized in kinetics studies to provide a means for continuous sampling of the liquid phases from systems in which a dispersed particulate phase is suspended in the liquid phase. In one application sampling equipment is being developed for in vitro study of calcium ion transport and calcium-ATPase activity in suspension of sarcoplasmic reticulum vesicles prepared from homogenates of rabbit muscle. In a second application a study of the mammalian blood-brain-barrier permeability is being aided by the development of an apparatus incorporating a sampler in an arteriovenous ex vivo shunt. In the latter plasmapheresis application, pooling of the plasma filtrate yields a single sample from which the plasma concentration times time integral can be evaluated for a chemical administered to the animal. Such sampling systems can be useful for the study of the kinetics of other fluid phase systems for which a membrane can be found that is permeable to one chemical of interest but impermeable to another necessary reagent or sink. Thus, other applications might be found in the areas of enzyme kinetics, pharmacokinetics, and the membrane transport of vesicle and cell suspensions.

Objectives: The principal objective is the development of the capability for fluid sampling based upon synthetic membrane technology. In many potential applications sampling by filtration or ultrafiltration may be more appropriate than alternative sampling techniques. Ultrafiltration membranes allow the formation of samples representative of the free concentration of small soluble substances. These membranes will retain within the system under study macromolecules and those substances which are bound to them as well as colloidal or cellular components of the system. Other applications may call for the use of larger pore diameter membranes if, for example, macromolecules are to be sampled as well.

Methods Employed: The sampling system generally consists of three elements: (1) a module or modules containing sampling membranes, (2) sample collection equipment, and (3) a means for controlling the rate of production of sample. The membrane module is designed so that the membrane forms a part of the wall of the channel through which the liquid to be sampled flows. Only a small fraction of the liquid is diverted across the membrane to form the sample. The sample is produced as a consequence of a difference in pressure imposed across the membrane. The rate of production of the sample is regulated either by controlling the transmembrane pressure difference or through use of a sample metering pump.

Significance: Membrane sampling is being applied to studies of the transport of calcium ions across sarcoplasmic reticulum (SR). The transport studies are performed in vitro on a suspension of SR vesicles in buffer; the vesicles being created by homogenizing rabbit muscle. The kinetics of calcium uptake by or efflux from the vesicles can be followed by monitoring the appearance or disappearance of calcium from the suspending medium. Also, changes in levels of ATP and inorganic phosphate can be used to infer the kinetics of the calcium dependent membrane ATPase. The membrane in the sampler retains the vesicles (which are thought to be in the range of 0.1-0.5 um in diameter), so that the sample is representative of the suspending media.

A second application concerns in vivo studies of exchange of substances between blood plasma and brain tissue across the blood-brain-barrier. The objective of developing a membrane sampling scheme in this application is to permit the determination of transport coefficients for the exchange process in cases for which alternative sampling techniques are not applicable or would be less accurate or less convenient. The transport coefficient, like permeability, depends upon the chemical substance employed. A particular category of substances for which membrane sampling would be attractive is the group of substances which are sequestered intracellularly in the brain, for example, potassium ion. Within this grouping there are three subsets for which alternative sampling techniques could be less attractive. One subset consists of substances with intermediate rates of equilibration between plasma and blood cells. Blood sampling techniques require an additional step of separating the plasma from the blood cells subsequent to withdrawing. Such a two step process for obtaining plasma samples will not yield accurate plasma concentrations if significant exchange between plasma and blood cells occurs before the separation step is effected. A second subset consists of substances for which the distribution kinetics are very rapid. Here continuous sampling techniques, like membrane sampling and continuous blood withdrawal would be preferable to discrete sampling techniques, like serial blood sampling. A third subset consists of substances which are subject to significant binding to plasma proteins. In order to follow free plasma concentrations in the animal as a function of time, the equilibrium binding curve has to be known and possibly also the kinetics of binding and dissociation. With membrane sampling this may be obviated by use of an ultrafiltration membrane for production of a protein-free plasma sample.

The membrane sampling technique can be applied to other acute pharmacokinetic studies which require the determination of the plasma concentration versus time integral.

Major Findings: Previously we determined the precision with which the concentration-time integral could be measured by membrane sampling in vitro under well controlled time varying conditions. We also showed that under conditions simulating the in vivo brain uptake experiments, diffusional transport of marker substance across the sampling membrane seemed not to contribute noticeably compared to the desired convective transmembrane transport.

During the present year we concluded two series of in vivo experiments using rabbits. These experiments were designed to compare the results obtained by membrane plasma sampling to results obtained by serial blood sampling and continuous blood sampling. Several radiolabeled compounds were used (water, sucrose, urea, butanol) for which all three sampling techniques ought to be valid. Comparable results were obtained by the three sampling techniques in these validation studies.

Current Activities: We are evaluating several non-metabolized marker substances to find one whose plasma-to-blood cell equilibration time constant is of the order of one minute. The chosen compound will be employed to test the hypothesis that membrane plasma sampling would be appropriate for the subset of substances with intermediate equilibration kinetics, whereas the whole blood sampling techniques would not.

A preliminary report was presented at the 2nd Tutzing Symposium, "New Membranes in Medical Treatment", September 14-17, 1981, Tutzing, West Germany. Approval and funding has been obtained from the Scientific Affairs Division of the North Atlantic Treaty Organization to administer a two-week intensive course entitled, "An Advanced Study Institute on Synthetic Membranes" during the summer of 1983 in Portugal.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10064-03 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Indirect Blood Pressure Measurements in Laboratory Animals Using Oscillometry

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. C. Walker	Mechanical Engineer	ACES BEIB
	J. E. Pierce	Chief, LAMSS	OD NHLBI
OTHER:	H. W. Tipton	Mechanical Engineering Tech.	ACES BEIB

COOPERATING UNITS (if any)
OD-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering and Applied Clinical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.0	OTHER: 0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Presently there are no reliable indirect methods of measuring blood pressure in dogs. Traditional techniques, used in humans, are unsatisfactory primarily because they require the placement of a transducer over the artery being monitored.

Because of the unreliability of traditional techniques we have been investigating a technique called oscillometry. Oscillometry is the method of measuring blood pressure by analyzing the pulse pattern of the cuff pressure oscillations.

In practice, a cuff is placed around a limb and inflated to a pressure above systolic and then slowly deflated. While the cuff is being deflated the amplitude of oscillation in cuff pressure, produced by the arterial pulse beneath the cuff, is monitored. Systolic and diastolic transitions in the oscillometric waveform are then used to indicate the indirect systolic and diastolic pressures respectively.

Objectives: The primary objective of this project is to develop an instrument to indirectly measure peripheral arterial blood pressure in laboratory animals.

Methods Employed: A model of the oscillometric process is currently being employed to develop and test an automated oscillometric instrument. The model consists of a simulated artery, cuff, sinusoidal pressure generator, and a Tektronix 4052 computer.

Significance: Animial surgery labs and other laboratories or veterinarian offices could use an indirect device on a daily basis. For various laboratory studies monitoring blood pressure in awake animals is very desirable, particularly with protocols involving atherogenic diets, and drug therapy. Another area of application would be in screening animals for hypertension research. For surgical procedures, an indirect technique will allow blood pressure monitoring before and during induction of anesthesia.

Major Developments: Based upon the model, improved schemes for detecting the systolic and diastolic transitions have been developed. The various hardware elements are being configured concurrently with software design. The oscillometric pressure detection algorithms are still under development with current efforts directed towards artifact rejection.

Proposed Course: Future efforts will be directed towards algorithm completion and incorporation of several unique features which are presently unavailable.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10065-03 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Transient Response of Micro-Calorimeters Using R-C Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. P. Mudd	Biomedical Engineer	BEIB, DRS
OTHER:	R. L. Berger	Section Chief	LTD, NHLBI

COOPERATING UNITS (if any)

LTD, NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation Branch

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.45	PROFESSIONAL: 0.45	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The behavior of heat conduction calorimeters lies between that of true adiabatic or bomb calorimeters and isothermal calorimeters. The use of an R-C model of the calorimeter and the application of Laplace transforms has enabled us to predict the response to a variety of inputs. With this model, we have identified the air gap between the cell and cell holder as a major source of error in thermo-kinetic measurements. We also used the model to design a new sensor/cell system which (a) eliminates the air gap, (b) increases sensitivity with no significant increase in risetime, and (c) accepts all three currently used cell sizes, 0.3, 0.5 and 1 ml.

PHS-6040
(Rev. 2-81)

Objective: The objective is to use the previously developed R-C model of the calorimeter as a design aid in overcoming and eliminating problems revealed by the model.

Significance: The model agreement with experimental data for pulse and step inputs is within 5%. With the model, we were able to redesign and evaluate, on paper, a new design for the sensor, cell, and mounting geometry. The new design achieves the following:

(1) It eliminates the air gap between the cell and cell holder which the model revealed to be a major source of error when the calorimeter was used in kinetic studies.
(2) It rearranges the geometry of the thermopile sensor in such a way that the same heat flow through the thermopile now produces a three-fold increase in signal level with no significant increase in rise-time.
(3) It utilizes only one sensor which allows the use of three cell sizes in the same calorimeter.

Proposed Course: The preliminary experimental results indicate that the new calorimeter design will achieve the performance predicted by the model. The single sensor design has also removed several restraints in cell design and will enable us to design a new cell with improved thermal characterstics and reliability.

Publications

"An optimized differential heat conduction solution micro-calorimeter for thermal kinetic measurements", C. Mudd, R.L. Berger, H.P. Hopkins, W.S. Friauf and C. Gibson, Journal of Biochemical and Biophysical Methods, 6, 1982.

"An new differential micro-calorimeter with nano-mole sensitivity for thermokinetic studies in biology", C. Mudd, R. L. Berger, and N. Davids, presented at FASEB meeting American Society of Biological Chemists, April 18-23, 1982, New Orleans.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10066-03 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Egyptian Training Project

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. P. Mudd	Biomedical Engineer	BEIB DRS
OTHER:	H. W. Metz	Assistant Branch Chief	SES BEIB DRS

COOPERATING UNITS (if any).
RIS, BEIB, DRS

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.45	PROFESSIONAL: 0.45	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The development of a system for transferring the training of Egyptian engineers in equipment repair from NIH to Egypt. The goal is a completely self-sufficient training center in Egypt for recruitment and training of scientific equipment repair personnel. This project is specifically concerned with the development of courses in basic instrumentation, electronics and troubleshooting for scientific equipment.

Objective: During Phase I of this project, several repair centers were organized and set up in Egypt. The personnel were brought to NIH for training and then sent to the centers. In Phase II, the emphasis will be on developing a facility in Egypt which assumes the training role. At the end of Phase II, the facility should be completely self-sufficient and staffed with Egyptian training personnel.

Significance: At the conclusion of Phase II, the role of NIH in the training process will end and the Egyptian facility must be capable of operating independently.

Proposed Course: Condensed, preliminary versions of the training courses were presented in Egypt in March-April and June of 1982. These trial courses were presented in order to determine: (a) the suitability of the course material, (b) an appropriate mechanism for the presentation of the material, (c) an appropriate laboratory evaluation technique for the students and (d) identification of possible trainees for the Egyptian presentation of the course.

From these courses, we will prepare the full length courses in cooperation with the selected Egyptian trainees during FY 82-83.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10073-03 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Secondary Emission Mass Spectrometer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Scientist	BEIB DRS
OTHER:	S. Markey	Chemist	LCS NIMH
	H. Fales	Laboratory Chief	NHLBI

COOPERATING UNITS (if any)

LCS NIMH and NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 1.2	PROFESSIONAL: 1.2	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Secondary Emission Mass Spectrometer (SEMS) is designed and assembled. It is anticipated that the facility will contribute to research programs in a number of Institutes, specifically NIMH (S. Markey) and NHLBI (H. Fales). The SEMS has the following features: (a) Ultra-high vacuum chamber with ultimate vacuum better than 10^{-9} torr; (b) Rapid linear motion multi-specimen holder permitting reflection and transmission mode of operation; (c) Energy analyzed ion gun (.05-10 keV) with deflector, pulser, and rastering. The gun is switchable to ions only or neutrals only modes of operations; (d) SIMS mass spectrometer in both reflected and transmission SIMS; (e) MS/MS/collision cell double quadrupole tandem system; (f) Secondary electron emission cell for negative ion studies; (g) Electron bombardment gun (.05-1.5 keV); (h) Flexible multi-flange system which will allow testing of various designs of ion sources and ion guns.

The SEMS permits us to study secondary emission processes on various surfaces under bombardemnt by electrons, ions, and neutrals in connection with ionization of biological compounds of high molecular weight. Development of analytical techniques based on Particle Induced Ionization Mass Spectrometry using SEMS for peptide sequencing analysis is planned for FY 1982-1983.

LaB_6 Cathodes Development

We continued to study the possible application of lanthanum hexaboride as an emitter for mass spectrometry ion sources. Experimental work primarily concentrated on life tests of a single-crystal LaB_6 cathode. Our results suggest that the life-time for LaB_6 in the vacuum 10^{-5} Pa or better is at least an order of magnitude longer than that of Re filament currently used in ion sources. In addition there is an obvious advantage of LaB_6 in terms of the efficiency of ionization when used with the Chemical Ionization ion sources.

Application of Fast Atom Bombardment in High Resolution Mass Spectrometry

Other activity under the project involved the conversion an AEI MS-9 mass spectrometer for FAB application by mounting an ion (neutral) gun on the available mini-flange using specially constructed adapter to 2 3/4" Conflat flange, making modification to the AEI ion source and to the direct insertion probe. Several alternative guns are being investigated including a saddle-field gun, capillaritron and hollow-discharge gun. The capillary neutral gun has been designed and fabricated for this application. High resolution mass spectra of peptides, triglycerides and glucuronides will be investigated using this technique. Similar modifications to Finnigan 3000 and VG70-70 mass spectrometers are under investigation.

Publications

Kelner, L., Fales, H., Markey, S. and Crawford, C.: Application of LaB_6 cathodes in mass spectrometry, International Journal of Mass Spectrometry and Ion Physics. (In press).

Kelner, L., and Lundquist, T.: Secondary Emission Mass Spectrometer. Proceedings of 9th International Mass Spectrometry Conference, Vienna, 1982 (In press).

Kelner, L., Markey, S.P., Fales, H.M. and Crawford, C.: Filaments for Ion Sources. Proceedings of 9th International Mass Spectrometry Conference, Vienna, 1982.

Friedman, M.H., Yergey, A.L., Campana, J.E., and Kelner, L.: Fundamentals of Ion Motion in Electric Radiofrequency Multipole Fields. U.S. Army MERADCOM, Fort Belvoir, VA, Report 2332, 1981.

Friedman, M.H., Campana, J.E., Seeliger, E.H., Kelner, L. and Yergey, A.L.: The Inverted Pendulum: A Mechanical Model of the Quadrupole Mass Filter. International Journal of Mass Spectrometry and Ion Phys. (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10074-03 BEI

PERIOD COVERED
October 1, 982 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Study of analytical applications of QUISTOR

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Scientist	BEIB DRS
OTHER:	S. P. Markey	Chemist	LCS NIMH

COOPERATING UNITS (if any)
LCS NIMH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Microanalysis Group

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .10	PROFESSIONAL: .10	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The QUISTOR special Quadrupole RF Power Supply was designed and fabricated by Extranuclear Laboratories, Inc. and delivered to NIH in May, 1982. The High Q head for the QUISTOR is adjusted to couple this device with the QPS and Triax flange of the quadrupole mass spectrometer. Additional pulse electronics will be required to initiate the study of storage capabilities of QUISTOR (approximately $22,000).

Development of a three-dimensional ion store and its application to mass spectrometry may result in improvements of detection capabilities of existing instruments and may increase limits of detection of compounds of biological interest.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10075-03 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Development of a new method of resolving power measurement

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	L. Kelner	Visiting Scientist	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Microanalysis Group

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .20	PROFESSIONAL: .20	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A simple method for determining the resolving power of low resolution mass spectrometers (specifically quadrupoles) has been developed. The method can be used in all types of mass spectrometers and with different ionization techniques (electron impact, chemical ionization, field ionization, particle induced ionization, etc.). The inlet system for DCB and DBB has been designed. Decachlorobiphenyl and decabromobiphenyl are used in this method as reference compounds to determine the resolving power of the mass spectrometer. These compounds can also be used for high mass sensitivity test on quadrupole mass spectrometers.

Publications

Kelner, L. and Rosenthal, D.: Reference Compounds for the Determination of Resolving Power. Proceedings of the 28th Conf. on Mass Spec., ASMS, 1980, p. 329.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10076-03 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Elemental Analysis of Microdroplets

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A.F. LeRoy	Chief, Analytical Methods Section	BEIB DRS
OTHER:	N. Roinel	Chemist	CEN, France

COOPERATING UNITS (if any)

Department of Biology, Centre d'Etudes Nucleaires, Saclay, France

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Analytical Methods Section, BEIB

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The principal instruments used in this project are the Cameca MBX 2-50 KeV scanning electron beam microprobe and a Cameca MS-46 electron microprobe, each equipped with two wavelength dispersive spectrometers. Quantitative elemental analysis in volumes of the order of 10^{-10} liter are possible using these instruments. The signal for some elements changes with time as a function of beam current-density, sample mass thickness and some other characteristics of the samples. A systematic quantitative study of the variables that affect stability of the signal has been undertaken to establish the ranges of values of these variables that permit usable results to be obtained.

Objectives: To establish the ranges of instrument operating conditions that yield stable signals for the elements analyzed with the MBX microprobe.

Methods Employed: Mathematical analysis of data obtained on representative microdroplets to quantify dependence of element X-ray signal on operating conditions as a function of time.

Significance: To provide a sound basis for quantitative analysis of microdroplets.

Proposed Course: To extend the number of variables included in the study to include temperature of the sample analyzed and the sizes of crystals analyzed.

Publication

LeRoy, A.F., Roinel, N. "Radiation Damage to lyphilized Mineral Solutions During Electron Probe Analysis: A Quantitative Study of Chlorine Loss as a Function of Beam Current-Density and Sample Mass Thickness", Journal of Microscopy, pp. , (1982).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10081-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Photo-Irradiation of Cancer Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PIs:	P. Smith	Visiting Scientist	BEIB DRS
	P. Ebert	Research Chemist	VB NCI
OTHERS:	R. Bonner	Physicist	BEIB DRS
	D. Tschudy	Senior Investigator	MET NCI
	J. Costa	Staff Physician	CNB NIMH
	R. Hess	Research Chemist	MET NCI

COOPERATING UNITS (if any)
VB-NCI;MET-NCI;CNB-NIMH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.7	OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The effect of various wavelengths of light has been studied for the relative effectiveness in killing leukemic L1210 cancer cells incubated with hematoporphyrin. Investigations were performed on the enhancement of the photo-induced killing of L1210 after pre-incubation of the cells containing succinyl acetone which is known to argument the uptake of heme and hematoporphyrin by cells. Increasing serum concentration in the medium was found to have protective effect on growth inhibition.

Objectives: To establish dose levels of the illuminating light required to produce various reductions in viable cell population. To determine the relative merits of enhancers which stimulate hematoporphyrin uptake by L1210 cells in photo induced killing.

Methods Employed: A lantern slide projector was modified to provide an illuminated 2" by 2" area suitable for exposing the flasks containing the L1210 cells. Provision was made for insertion of interference filters at specific wavelengths corresponding to absorption peaks for hematoporphyrin (397 nm, 503 nm, 531 nm, 621 nm, and 636 nm) and also for accommodating heat rejection filters. Exposure levels of the illuminating light were measured using a commercial (EG & G) radiometered. Typical levels are 3 mw/cm^2. Exposure times ranged from less than one minute to 30 minutes.

Major Findings: The in vitro studies performed have demonstrated that L1210 cells are killed by light if they are previously incubated in the presence of hematoporphyrin (HP). Plots of log cell count vs. time show a linear increase in time for the non-illuminated control and a fall in cell count for two days followed by subsequent growth in parallel with the control for the illuminated cells. For lethal doses of illumination this growth does not resume. The effectiveness of the killing was determined by measuring the ratio of the curves after resumption of growth. HP was rapidly taken up by L1210 cells to near maximum levels (5mM) within 10 minutes. Although uptake of HP is rapid and intracellular levels were sustained for up to 1 day, increased killing of L1210 cells with HP by light was observed with increasing lengths, up to 1 day, or pretreatment of cells with HP before exposure.

Pretreatment of cells with succinylacetone (SA), a drug which enhances the uptake of heme and HP into L1210 cells, decreases the requirement for either light of HP dose to kill tumor cells. Incubation of cells with 2mM SA for 3 days prior to treatment with HP produced a 7 fold decrease in the number of surviving cells with respect to a control population after an equivalent light dose of 12 minutes. In the presence of a fixed amount of HP in the medium, increasing serum concentration exerted a protective effect against growth inhibition produced by light. This probably results from diminished uptake of HP to cells, as well as an augmented loss of porphyrin, because of increased HP binding to serum proteins.

The following order of 503, 397, 531, 621, and 636 nm was found for the relative efficiency of specific wavelengths for equivalent exposures in killing L1210 cells. This order corresponds to the order of decreasing absorption of the peaks in the HP spectrum except for the anomalous position of 397nm.

Significance: The findings with SA demonstrate that the natural affinity of tumor cells for HP can be increased by administration of certain chemical agents. It is possible that these chemical manipulations may augment HP uptake by tumors in vivo, allowing for improved visual diagnosis of malignancies and enhanced therapeutic applications of HP in oncology.

Proposed Course: To study agents which have been shown to augment HP uptake and compare the photoinduced killing of L1210 cells to that attained with SA. To establish a suitable model for in vivo work with mice.

Significance: Phototherapy is becoming a course of treatment for certain types of cancer. By establishing wavelength criteria and enhancing the light effect, improved photo-therapy will be made possible.

Proposed Course: To extend the in vitro studies to in vivo work. Initial studies will be performed on mice.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10082-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Protein Sequencer Modification

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.J. Lutz	Chemical Engineer	BEIB DRS
OTHERS:	E. Appella	Research Scientist	LCB NCI
	L. Robinson	Physical Scientist	LCB, NCI
	R. L. Dedrick	Chief	ChES, BEIB, DRS
	J. K. Inman	Chemist	LI, NIAID

COOPERATING UNITS (if any)
LCB/NCI, LI NIAID

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Chemical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Md. 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 1.75	OTHER: .25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Proteins serve an incredible variety of biological functions which are determined indirectly by the amino acid sequence in the protein. The most effective single method for sequence determination is the degradation technique of Edman, which is performed by an automated instrument manufactured by Beckman. By a repetitive sequence of processes, amino acids are chemically cleaved one by one from the N-terminal end of a large protein or polypeptide. Recently, proteins of considerable interest are being isolated only in minute quantities, too small for accurate determination on available automated instruments. The goal of our project is to discover improvements to the present protein sequencing methodology that will allow for "microsequencing." The present emphasis is on improvements in the design of the automated sequencer. The three main features in the design that require improvements are (1) reagent and solvent delivery valve mechanism, (2) vacuum system, (3) automatic conversion of cleaved amino acid to a more stable phenylthiohydantoin derivative for analysis.

Major Findings: At present, all of the proposed modifications to the Beckman spinning-cup sequencer have been implemented: the liquid N_2 cold-trapped vacuum system, the new delivery values, the modified spinning cup chamber, and the automatic converter. The new unit is undergoing testing. Initial results showed very low repetitive yield (85%). Investigation showed a small leakage of some reagent and solvent vapors through the delivery value line into the spinning cup at inappropriate times. Also, the volume of delivery of cleavage acid was slightly low, thereby not covering the entire protein film in the spinning cup. Steps have been taken to correct these deficiencies. The most recent runs have given 95% to 96% repetitive yields with low background noise and little carryover from cycle to cycle. The machine is to be tested with smaller samples of 1 to 10 nmoles protein.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10091-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Mechanics of Red Blood Cell Membrane

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. R. Markle	Biomedical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .1	PROFESSIONAL: .1	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A micromanipulation system consisting of an inverted microscope, two micromanipulators and video equipment necessary for the recording and analysis of data has recently been acquired. This system will be used to investigate the intrinsic material properties of red cell membrane, such as the elastic shear modulus, area compressibility modulus, membrane viscosity, etc., and large lipid vesicles using micropipette aspiration and flow channel techniques.

PHS-6040
(Rev. 2-81)

Methods: Presently both micropipette aspiration and flow channel techniques are being developed and will be used in the above studies. However, the system is flexible and can be readily adopted to the needs of any specific experiment.

Proposed Course: Initially the system will be used to investigate the intrinsic material properties of red cell membrane in diseased states. At the present time red blood cells obtained from sicle cell patients are of primary interest. However, red cells from patients with diabetes and muscular dystrophy, etc. are also of interest and will be studies. Other uses of this system may include studies of cell lysis during the freezing and thawing process used in blood storage, measurement of the affinity of red blood cell membranes for particle surfaces, and measurements of the mechanical properties of both pure and multiphase vesicle systems.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10095-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Multiple Probe pH Measurement System for Canine Myocardium

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. Markle	Biomedical Engineer	MES BEIB DRS
OTHER:	D. McGuire	Mathematician	MES BEIB DRS
	S. Goldstein	Chief	MES BEIB DRS
	R. Patterson	Senior Investigator	NHLBI

COOPERATING UNITS (if any)
Cardiology Branch, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 202305

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.5	OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER
☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

For the past several years, considerable effort has been expended on the development of a miniature fiber optic pH probe for physiological use. With the first generation of probes and support equipment the feasibility of optically measuring pH via a pH sensitive dye was demonstrated and many subtleties associated with the probe construction and use made apparent. With this knowledge an improved probe and multichannel support system was designed and constructed and is presently being used to measure pH in the wall of beating canine hearts. Within the last year further refinements in the probe design and construction have reduced its response time to a step change in pH while signal processing modifications have extended the range of the probe from .4 pH units (7.0 to 7.4) to 2.0 pH units (6.0 to 8.0). In addition, preliminary results indicate that LED's and photodiodes may be used with the new probe design.

Objectives: To reduce the response time of the probe to a step change in pH without compromising measurement accuracy and resolution, to extend the pH range over which the probe will operate, to reduce fabrication difficulties, and to determine if LED's can be used instead of a tungsten light source.

Methods Employed: The probe was redesigned such that only one of the two optical fibers is enclosed by the dialysis membrane. This allowed the use of a smaller diameter dialysis membrane and thus decreased the probe's response time. In addition the fiber diameters were increased from 0.075 to 0.125 mm (increasing the return signal from the probe) while only increasing the diameter of the probes stainless steel needle housing by 0.51 mm.

The pH range of the probe was extended by using a nonlinear function described by Peterson et. al. (1) which relates the measured light intensity returned from the probe to the pH of the probe's environment. Calibration of the probes with this relation requires the use of three known buffers since the function has three unknown constants.

Significance: At the present time this is the only system available to measure tissue pH in vivo and on line. Such information is of use to experimental cardiologists interested in evaluating drugs which affect tissue perfusion, obstetricians interested in monitoring fetal scalp pH and biomedical researchers in general.

Proposed Course: To further improve the reliability and ease of operation of the system and to reduce its size and cost.

Publications

(1) Peterson, J.I., Goldstein, S.R., Fitzgerald, R.V. and Buckhold, D.K., "A Fiber Optic pH Probe for Physiological Use," Analytical Chemistry, May 1980, pp. 864-869.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10096-02 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Light Scattering Method for Evaluation of Platelets

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.F. Bonner	Physicist	BEIB DRS
OTHERS:	T.R. Clem	Electrical Engineer	BEIB DRS
	S.B. Leighton	Mechanical Engineer	BEIB DRS
	J. Fratantoni	Director, Blood Bank Products	BB FDA
	B. Poindexter	Biologist	BB FDA

COOPERATING UNITS (if any)

Bureau of Biologics, FDA

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ■ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Assessment of the functional status of platelets for transfusion is confounded by the inherent complexity of the cell, as well as the intricate requirements of sample preparation. A correlation between discoid shape and functional integrity of the platelet has been established. We have developed a complex automatic machine based on previous experiments with a simple prototype which measures the fraction of the platelets that are discoid and the optical (volume) concentration of unaggregated platelets in standard blood bank platelet concentrate units within their bags. The microprocessor based instrument automatically determines the volume concentration of unaggregated platelets and the fraction that are fully viable (discoid) in 3 minutes from simple insertion of the blood storage bag in a slot. This process is noninvasive (sterile) and nondestructive. Thus it allows frequent measurements on the platelets prior to transfusion in order to optimize the quality and quantity of transfused platelets given patients. It also allows accurate investigations for optimizing storage and preparation methods.

Objectives: Develop an optical method to evaluate platelets in standard blood storage bags and design and construct a practical clinical instrument using this noninvasive optical method.

Methods: Measurement of a large number of platelet concentrates on a simple prototype optical instrument in parallel with biochemical and visual grading provided a basis for the evaluation of the light scattering method. Light scattering theory applied to this data base led to the understanding of effects of the platelet number density and fraction that are discoid. This theoretical understanding provided the basis for the design parameters of the automatic instrument as well as its ability to automatically convert the raw optical signals into the desired concentration and viability fraction. It allows the use of the instrument with all the different types of commercial blood storage bags.

Major Findings: The automatic instrument can be used routinely by relatively unskilled technicians to evaluate quickly, noninvasively and nondestructively the quality and quantity of platelets in any standard storage bag. In preliminary tests the accuracy appears to as good or better than that of the present invasive measurements not routinely allowed for a product to be transfused.

A newly developed multiple scattering theory very accurately predicts the optical scattering effects, which suggests further application to many types of concentrated cell suspensions.

Significance: This method and instrument may allow for the first time the optimal utilization of the blood bank product (platelet-rich plasma) for transfusion. It allows continuous quality control of the preparation and storage of the platelet concentrates at blood banks and hospitals. It may prove to very useful in assessing new methods of preparing and storing the blood product for transfusion.

Proposed Course: Further testing and refinement of the automatic platelet assessment instrument is in progress to insure accuracy with wide variety of bag types and with samples contaminated with red blood cells and lymphocytes. Use in clinical setting (NIH Blood Bank) is planned in the near future to insure trouble-free routine operation. Multicenter trials to assess potential of device to improve quality and dose of platelets transfused into patients will follow successful completion of the above steps.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10097-02

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Mechanics of the Left Ventricle

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. S. Chadwick	Biomedical Engineer	BEIB DRS
OTHER:	R. Patterson	Senior Investigator	Cardiology NHLBI

COOPERATING UNITS (if any)

NHLBI-Cardiology Branch

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A theoretical analysis of the mechanics of the left ventricle has been undertaken in which the myocardium is modeled as a fluid-fiber continuum. A time dependent length-tension relation is applied to the three-dimensional architecture of the myocardium. The anisotropic elastic behavior is crucial to understanding the contractility of the myocardium, the development of systolic pressure, pumping of blood out of the ventricular chamber, and the flow of blood in the myocardium itself.

Objectives: To develop a quantitative theory which describes the mechanical events in the left ventricle throughout the cardiac cycle.

Methods Employed: The myocardium is idealized as a continuum of muscle fibers imbedded in an incompressible fluid. The fiber direction field measured by Streeter is an essential part of the theory in which a pressure field develops in the tissue to support the tensile stresses which act along the fiber directions. Boundary value problems are formulated for the various phases of the cardiac cycle.

Major Findings: Solutions have been obtained so far in a finite cylindrical model of the left ventricle. Some interesting results already emerge from the analyses, e.g. the isometric contraction in a muscle preparation is not equivalent to the isovolumic contraction phase of the heart. Also the physiological distribution of fiber angles appears to maximize the development of systolic pressure. The theory also supports the empirical time varying elastance model of Sugawa.

Significance: Further development of the theory will help in the understanding of ventricular hypertrophy, and help to quantify contractility which is an important index in the assessment myocardial ischemia.

Proposed Course: A more realistic ventricular geometry will be considered, and an analysis of myocardial blood flow will be undertaken.

Publications:

Chadwick, R.S.: The Myocardium as a Fluid-Fiber Continuum: Passive Equilibrium Configuration. 1981 Advances in Bioengineering, ASME.

Chadwick, R.S.: Mechanics of the Left Ventricle, Biophysical Journal, 1982 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10098-02 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Laser Instrumentation for Vitreous Surgery

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. F. Bonner	Physicist	BEIB DRS
OTHERS:	S. M. Meyers	Senior Staff Ophthalmologist	CB NEI
	S. B. Leighton	Mechanical Engineer	BEIB DRS

COOPERATING UNITS (if any)

Clinical Branch, NEI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.80	PROFESSIONAL: 0.80	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A carbon dioxide laser with a special fiber optic delivery system for use in vitreous surgery has been developed and is undergoing testing in animals. Preliminary data reveal that the carbon dioxide laser instrument appears beneficial in certain aspects of vitreous surgery.

Objectives: This study is designed to develop and test the efficacy of a carbon dioxide laser instrument for use in vitreous surgers.

Methods Employed: A carbon dioxide laser with a special delivery system adapted for use in vitreous surgery is being developed. The safety and efficacy of the prototype unit is being tested in rabbits and monkeys with vitreal membranes. The vitreal membranes in these animals are created using standardly accepted methods. The findings are documented with photography. The animal eyes are examined clinically and pathologically at selected times after surgery.

Major Findings: Preliminary data reveals that the carbon dioxide laser can cut experimentally created membranes in rabbits. During the development of this carbon dioxide laser instrument, combined illumination-irrigation 20-gauge probes for vitrectomy in humans were built. These vitrectomy instruments performed well in human cases and are currently being used in all human vitrectomy cases at the National Eye Institute.

Significance: Although the present mechanical vitrectomy instruments perform well in most cases, there is a risk of intraoperative complications (retinal tears and hemorrhage) when vitreal membranes are cut, especially if the membranes are taut and have a strong adhesion to the retina. "Tension" on the membranes is increased as the "cutter" of the vitrectomy instrument or the vitreous scissors cuts the tissue. This tension is transmitted to the vitreoretinal adhesion and surrounding retina predisposing this area to hemorrhage and retinal tears. If the vitreal membrane is vascularized, this tension may cause bleeding. The carbon dioxide laser vitrectomy may decrease the incidence of these intraoperative complications and increase the facility in cutting selected vitreal membranes.

The fiber optic delivery system for the CO_2 energy as well as the specific laser pulse pattern developed for optimal cutting of vitreous bands without damaging surrounding eye tissues may be generally applicable to all types of CO_2 laser surgery. The combined illumination-irrigating 20-gauge probes have improved the currently available instrumentation available for vitreous surgery.

Proposed Course: If further investigation of the prototype carbon dioxide laser in animals documents the efficacy and safety of the instrument in vitreous surgery, a clinical trial in selected patients undergoing of vitreous surgery will be initiated.

NEI Research Program: Retinal and Choroidal Diseases — Diabetic Retinopathy, Sickle Cell Retinopathy, and Other Vascular Abnormalities/Retinal Detachment and Vitreous Disorders.

Publications:

Myers, S.M., Bonner, R.F., and Leighton, S.B.: Combined illumination-irrigation 20-gauge probes for vitrectomy. Arch Ophthalmol 100:622-623, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10099-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Cochlear Mechanics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI: R. S. Chadwick Biomedical Engineer BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.1	PROFESSIONAL: 0.1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

This study is concerned with theoretical analysis of the propagation of mechanical waves in the cochlea. These waves result from the input action of the stapes footplate and the subsequent interaction of the basilar membrane with the cochlear fluids. The stereocilia of the hair cells deform due to the wave motion and convert information contained in the waveform to electrical impulses. A quantitative understanding of the wave patterns and the mechanical factors affecting them is essential for an understanding of the hearing process. The influence of cochlear geometry, fluid and membrane viscosity, and elastic coupling in the basilar membrane are being studies.

Objectives: To calculate the velocity and pressure field in the cochlear fluids, and the displacement field of the basilar membrane, in response to various types of physiological input sounds.

Methods Employed: The appropriate equations of fluid and solid mechanics are written in linearized form to obtain the basic hydroelastic boundary value problem. This problem is then solved using a variety of methods of asymptotic analysis. The basic small parameter is the slenderness of the cochlear geometry. Low and high frequency limits are studies, as well as the effects of elastic anisotrophy of the basilar membrane.

Significance: The ear has the ability to distinguish different tones with high sensitivity. One outstanding question in auditory physiology is whether the main auditory analysis is performed mechanically or by neural means. Theoretical calculations of the type being done in this project will help to answer this question.

Proposed Course: A study of the micromechanics of Organ of Corti is planned, as well as the electro-mechanics of the hair cell transduction process.

Publications

Chadwick, R.S.: Studies in Cochlear Mechanics. Lecture Notes in Biomathematics, in Proceedings of NSF-CBMS Regional Conference on Mathematical Modeling of the Hearing Process 1980, Springer-Verlag, NY.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10100-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Mechanics of Muscle Contraction

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.S. Chadwick	Biomedical Engineer	BEIB DRS
OTHER:	R.J. Podolsky	Chief	LPB NIAMDD

COOPERATING UNITS (if any)

NIAMDD - Laboratory of Physical Biology

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An outstanding unanswered question in muscle physiology is concerned with the details of the molecular mechanisms involved in the generation of force. Physiological experiments on striated muscle aimed at obtaining information at the cross bridge level are often complicated by unwanted effects which make interpretation difficult. Some of these are nonuniform sarcomere lengths, end effects due to tendons and clamping, dispersion of fiber lengths, nonalignment of striations across the muscle cross section, and mechanical wave propagation effects. A continuum theory incorporating sarcomere interactions would be very useful in interpreting physiological data.

PHS-6040
(Rev. 2-81)

Objectives: To develop a continuum theory of striated muscle contraction incorporating sarcomere interactions for the resting, active, and rigor physiological states.

Methods Employed: As a first step, a one-dimensional theory will be developed which will incorporate the three distinct length scales which appear in the mechanical descirption of muscle contraction. Events at the cross bridge level occur on a scale of nanometers, those at the sarcomere level occur on a scale of microns, while the total length of the fiber is typically several millimeters. A fiber is composed of about 10^4 sarcomeres in series. The equations of motion and energy of a sarcomere involve the statistical mechanics and biochemistry of the cross bridge interactions and the interactions with nearest neighbor sarcomeres. The continuum limit of the equations of the chain yields a system of partial differential equations to be studied.

Significance: Mathematical solutions of the boundary value problems can simulate and lead to a better understanding of physiological experiments on muscle contraction.

Proposed Course: The one dimensional continuum theory has led to a coupled system of nonlinear partial differential equations. These equations must now be solved to simulate the physiological experiments.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10102-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Osmotic Behavior of Perfused Tissues and Organs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L.Levin	Biomedical Engineer	BEIB DRS

COOPERATING UNITS (if any)
MRC Medical Cryobiology Group, Cambridge University Department of Surgery, Cambridge, England

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
DRS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.20	PROFESSIONAL: 0.20	OTHER: 0.00

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the osmotic behavior of perfused tissues and organs during the introduction and removal of cryoprotective agents (CPAs) from both an analytical and an experimental point of view. Comparison of theoretical predictions of organ behavior during CPA introduction and removal based upon a newly developed non-steady-state mass transfer model with experimental observations of the responses of perfused organs to changes in the composition of their perfusates will-it is hoped-facilitate the development of optimum CPA introduction and removal protocols.

Objectives:

(1) To develop a non-steady state mass transfer model of the osmotic response of perfused tissue and organs to the introduction and removal of cryoprotective agents.

(2) To experimentally observe the osmotic response (i.e., changes in weight, vascular resistance and effluent composition) of isolated perfused organs to the introduction and removal of cryoprotective agents.

(3) To correlate our analytical and experimental findings and deduce the rate-limiting transport parameters.

(4) To develop optimum CPA introduction/removal protocols.

Methods Employed:

(1) Mathematical modeling and data analysis will be accomplished through the use of NIH's DEC-10 computing system and associated computer graphics facility.

(2) Experimental observations will be conducted with the aid of a microprocessor controlled organ perfusion system.

Significance: High concentrations of cryoprotective agents (CPAs) such as glycerol and dimethylsulfoxide are necessary for the successful cryopreservation of cells, tissues, and organs. Unfortunately, the introduction of CPAs prior to freezing and their removal after thawing has been documented in many instances to be as damaging as the freeze-thaw process itself. In order to help avoid the possible adverse osmotic effects observed by many investigators during CPA introduction and removal, a comprehensive theoretical and experimental analysis of the osmotic behavior of perfused tissue and organs is necessary.

Major Findings: Comparison of our preliminary theoretical and experimental results shows a large degree of both qualitative and quantitative agreement for the overall osmotic behavior of a perfused organ. Specifically, in both instances, (1) a lack of high molecular solute in the perfusate seems to cause a significant gain in weight, and (2) the initial weight gain during CPA removal is much greater than the initial weight loss and subsequent weight gain during CPA introduction. In addition, the theoretically observed changes in vascular resistance resulting from osmotically induced alterations in the thickness of the endothelial layer of the vasculature mimics the changes in vascular resistance observed experimentally. These numerous similarities suggest that our work should provide some indications as to the nature of the osmotic stresses and strains which might result in tissue or organ damage during CPA introduction/removal and therefore facilitate the development of optimum CPA introduction/removal protocols.

Proposed Course: To continue our current theoretical and experimental studies of the responses of perfused organs to the introduction and removal of cryoprotective agents. We will be concentrating upon fufilling the last two of the objectives listed above.

Collaborator: The experimental aspects of this project are being conducted in the laboratories of Dr. David E. Pegg, Chief of the MRC Medical Cryobiology Group, Cambridge University Department of Surgery, Cambridge, England.

Publications:

Levin, R.L. "The Osmotic Behavior of Perfused Tissues and Organs", 1981 Advs. in Bioengineering, pp. 131-134, 1981.

Levin, R.L. "Optimum Methods for the Introduction and Removal of Cryoprotectants: Perfused Organs", 1982 Advs. in Bioengineering, 1982. (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10103-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Triple Laser - Multi Parameter Flow Cytometry System for Study of Tumor Cell Kinetics

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	W. Schuette	Chief	ACES BEIB DRS
	S. E. Shackney	Acting Chief	CKS CPB DCT NCI
OTHER:	F. A. Plowman	Engineering Tech.	ACES BEIB DRS
	C. A. Smith	Med. Tech.	CKS CPB DCT NCI
	S. J. Occhipinti	Micro. Biol.	CKS CPB DCT NCI
	H. Mujagic	Visiting Scientist	CKS CPB DCT NCI
	S. S. Chen	Visiting Fellow	CKS CPB DCT NCI

COOPERATING UNITS (if any)

DRS - NCI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
National Institutes of Health

TOTAL MANYEARS: 3	PROFESSIONAL: 2	OTHER: 1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A triple laser flow cytometry system is being developed so that various imunofluorescent labeling techniques may be employed for the investigation of tumor cell kinetics. Three laser beams at different wave lengths will be made to intersect a tumor cell flow stream passing through a quartz cuvette so that multiparameter singnals may be obtained. These signals will be processed by specialized parameter signals may be obtained. These signals will be processed by specialized electronics and then analyzed by means of a PDP 11 computer.

PHS-6040
(Rev. 2-81)

Publications

H. Mujagic, C.E. Smith, W.H. Schuette and S.E. Shackney, "The Cell Tubulin Content Frequency Histogram Obtained by Flow Cytometry in Sarcoma 180 Cells In Vitro". Presented AACR, St. Louis, April 30, 1982.

W.H. Schuette, M.A. MacCollum, C.E. Smith, J.M.S. Prewitt and S.E. Shackney, "An Iterative Method for the Decomposition of DNA Histograms", Fifth Annual Meeting Cell Kinetics Society, Houston, Texas; March, 1982.

W.H. Schuette, S.E. Shackney, M.A. MacCollum, and C.E. Smith, "A High Resolution Method for DNA Histogram Analysis That is Suitable for Detection By Flow Cytometry (FCM) of Multiple Closely Spaced Aneuploid Cell Populations in Clinical Samples", Proceedings Engineering Foundation Society for Analytical Cytology; April, 1982.

B. Congee, S.J. Occhipinti, H. Mjagic, C.E. Smith, W.H. Schuette, S.S. Chen and S.E. Shackney, "Studies on the Lethal and Sublethal Effects of Vincristine (VCR) in Sarcoma 180 In Vitro, Proceedings Cell Kinetics Society; April, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10105-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Adaptation of an EPICS II Flow Cytometer for T. Cruzi Analysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. E. Hall	ACES, BEIB, DRS
	J. S. Dvorak	LPD NIAID

COOPERATING UNITS (if any)
LPD-NIAID

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .8	PROFESSIONAL: .7	OTHER: .1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An EPICS II Flow Cytometer is being used to perform cytometric analysis on a unicellular protozoan known as trypanosoma cruzi, the causative agent of Chagas desease. The EPICS II is composed of a fluid flow system for hydrodynamic focusing, a laser for excitation, signal processing electronics for data acquisition and a computer for data analysis. Developmental work is being carried out upon this system in order to improve the quality of the data acquired and the way in which it is analyzed. This includes modification of the various sensing systems to increase signal to noise ratio and the interfacing of a graphic display system in order to expand the data processing capability.

Publications

Dvorak, J.A., Hall, T.E., St. J. Crane, M., Engel, J.C., McDaniel, J.P. and Uriegas, R. "Trypanosoma cruzi: Flow Cytometric Analysis I. Analysis of Total DNA/Organism by Means of Mithramycin-Induced Fluorescence"

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10106-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Study of Fluorescein and Dextran Uptake in Tumors Using Chronic, Implanted Fiber Optic Probes

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. L. Levin	Biomedical Engineer	BEIB DRS
OTHER:	R. L. Dedrick	Chief, ChES	BEIB DRS
	D. McGuire	Mathematician	BEIB DRS
	S. Dellon	Chemical Engineer	BEIB DRS
	D. Brouns	Chemical Engineer	BEIB DRS
	P. M. Gullino	Chief	LPP NCI

COOPERATING UNITS (if any)
LPP-NCI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 2.0	PROFESSIONAL: 0.75	OTHER: 1.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Using an in vivo micro-fluorimetry system previously developed, we have employed carboxy fluorescein and fluorescently-tagged dextran tracers in an attempt to characterize the mass transport characteristics of solid tumors.

PHS-6040
(Rev. 2-81)

Objectives: To monitor and analyze the mass transport characteristics of solid tumors in order to facilitate the development of optimum drug modalities.

Significance: In growing tumors, the distribution of chemotherapeutic agents varies widely as a result of angiogenesis and necrosis. A quantitative understanding of mass transport in tumors is therefore essential for the development of optimum drug modalities. Unfortunately, common assay techniques requiring the dissection of tumors tend to mask these dynamic changes by yielding spatial distributions of marker substances at only a single instance of time. To facilitate the study of the transport properties of solid tumors under dynamic conditions, two new techniques have recently been developed. These techniques permit the direct in vivo long term monitoring of the concentration time course of fluorescently-tagged substances. This study involves the use of one of these techniques, namely, the in vivo microfluorimetry method previously developed in the laboratory, to monitor the transient mass transfer characteristics of solid tumors.

Major Findings and Proposed Course: Our preliminary results indicate that the transport of low molecular weight carboxy fluorescein is not "flow-limited" and that the transport of dextrans of molecular weights ranging from 20,000 to 150,000 daltons is not "membrane-limited". We are currently in the process of developing suitable transport models which will not only adequately describe our experimental findings but will also be capable of yielding values for the perfusion rate Q and the vascular permeability coefficient K. This involves deconvolving the system's effective impulse response characteristics from the measured input blood signal and output tissue signal using numerical techniques and then fitting the resulting transfer function to an N-compartment pharmacokinetic model.

Publications

Levin, R.L., et al.: "Tumor Transport Characteristics as Determined by In Vivo Microfluorimetry", 1982 AIChE Symposium on Transport Phenomena in Biomedical Systems, 1982 (in press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10108-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Thermodynamic Behavior of Cells and Tissues at Subzero Temperatures

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.L. Levin	Biomedical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.05	PROFESSIONAL: 0.05	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

During the past twenty years, numerous models have been proposed to describe the osmotic behavior of biological cells during freezing and thawing. Although these studies have pinpointed the important biophysical parameters governing the volumetric response of cells at subzero temperatures they all have one serious drawback. Namely, all of the current models deal with a single, isolated cell suspended in an infinite amount of bathing solution which is being cooled or warmed uniformly at a constant rate. No provision is made for those common situations where (1) the volume of cells is comparable to the volume of the suspending solution or (2) the cellular system is cooled or warmed in a non-uniform manner with time due to the inability of the freeze-thaw device to handle the large amount of latent heat generated during freezing or adsorbed during thawing. The purpose of the present study is therefore to analytically investigate cellular osmotic behavior under non-ideal, but typical, freeze-thaw conditions.

Objectives: To analytically characterize the behavior of biomaterials during freezing and thawing in order to facilitate progress in attempts to successfully freeze-preserve cells, tissues and organs.

Methods Employed: Mathematical modeling will be accomplished through the use of NIH's DEC-10 computing system and associated computer graphics facilities.

Significance: Cryopreserving biological materials such as blood, sperm and ova, skin and various other types of cells and tissues in research institutions and hospitals is a matter of great practical convenience since extremely low temperatures curtail metabolism and degenerative biochemical reactions. In fact, most biomaterials could probably be stored for milenia in a cryogenic environment. Unfortunately, in order to achieve this goal, cellular survival must be ensured during the critical cooling and warming periods associated with this form of storage. Consequently, further progress in the successful cryopreservation of cells, tissues, and organs necessitates an increased understanding of both the physical chemical events and the cellular responses that occur during a freeze-thaw cycle.

Major Findings: Our results indicate that the cytocrit of the cell suspension (Volume Cells/ Total Volume Suspension) begins to significantly affect cellular volumetric behavior at levels above 10%. This is especially true for pre-frozen cell suspensions which are being warmed at very high rates in which case the cells are exposed to strongly hypotonic conditions just after the complete melting of the extracellular ice. Our results also indicate that most of the cellular water loss during freezing or gain during thawing may occur during the long temperature-time plateaus which usually occur just after the initial formation of extracellular ice during cooling and just before the final melting of the extracellular ice during warming rather than at lower or high temperatures.

Proposed Course: To extend our analysis to systems containing high concentrations of cryoprotective agents.

Publications

Levin, R.L. "The Limiting Effects of Heat and Mass Transfer on the Osmotic Behavior of Cells during Freezing and Thawing", Cryobiology. (In press).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10109-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Adjunct Heat Treatment of Cancer

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. L. Levin	Biomedical Engineer	BEIB DRS
OTHERS:	D. Shook	Biomedical Engineer	BEIB DRS
	M. Hagmann	Senior Staff Fellow	BEIB DRS
	E. J. Glatstein	Chief	ROB NCI

COOPERATING UNITS (if any)
Bureau of Radiological Health, FDA, Rockville, MD

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.5	OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to facilitate the development of adjunct hyperthermia modalities for cancer by theoretically and experimentally studying the spatial and temporal variation in the temperature field of tissues subjected to microwave and radio frequency electro-magnetic radiation.

PHS-6040
(Rev. 2-81)

Objectives: (1) To optimize the microwave radiation fields generated by a "modified Fletcher-Suit" applicator; (2) To measure the spatial and temporal variation of the temperature field generated by the modified Fletcher-Suit applicator in various types of "phantoms"; (3) To develop a generalized mathematical model which will predict the spatial and temporal variation of the temperature field within a tissue or organ subjected to electro-magnetic irradiation; (4) To develop optimal adjunct hyperthermia modalities.

Methods Employed: The "Fletcher-Suit" applicator microwave field characteristics will be measured by employing various types of phantoms, thermographic cameras and a newly available electromagnetically insensitive fiber optic temperature probe. The mathematical modeling will be accomplished through the use of ROB's PDP 11/70 computing system and associated computer graphics facility.

Significance: At present the heat treatment of cancerous cells when combined with conventional radiotherapy and chemotherapy shows considerable promise in the management of cancer. Nevertheless, there still remain numerous importaant problems that must be resolved. Of paramount importance is the problem of generating and controlling uniform temperature fields within tissues. This study will therefore attempt to facilitate the development of optimum hyperthermia modalities by theoretically and experimentally studying the temperature fields within tissues subjected to microwave EM radiation.

Proposed Course: To begin characterization of newly available modified Fletcher-Suit applicator and development of a suitable mathematical model utilizing the "bioheat" transfer equation.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10110-02 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

A Dual 3-Dimensional Position Monitor For Speech Analysis: MOD. II

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	E. C. Walker	Mechanical Engineer	ACES BEIB
OTHER:	H. W. Tipton	Mechanical Engineering Tech.	ACES BEIB
	T. L. Talbot	Mechanical Engineer	ACES BEIB
	C. L. Ludlow		LCD NINCDS
	M. Dorn-Quine	Guest Researcher	NINCDS

COOPERATING UNITS (if any)
LCD-NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Applied Clinical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.0	2.75	.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Several speech monitoring instruments have been designed to study the etiology of normal and abnormal articular movements in humans. The first system, which is in current use, provided a unique method of monitoring 3-D lip and jaw movements. The second system, MOD II, is an improved version of the first. The device consists of two, mirror image, transducers mounted on a common head frame. Each transducer, which can be individually adjusted, is capable of measuring the movement of a point in three orthogonal planes. The transducers have been structurally and operationally redesigned to provide increased linearity, resolution, and reduced weight. Additionally, the head frame has been totally redesigned to provide improved wearing comfort and reduced weight. The improved system will facilitate studying a broader patient population such as children and the elderly.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10112-02 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Analysis of Microcirculatory Blood Flow by Laser Doppler Scattering

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R.F. Bonner	Physicist	BEIB DRS
OTHERS:	R.L. Bowman	Laboratory Chief	LTD NHLBI
	P.D. Bowen	Biologist	LTD NHLBI
	A. Tahmoush	Consultant	NB NINCDS
	M. Kaliner	Section Chief	LCI NIAID
	H. Druse	Clinical Assoc.	LCI NIAID
	C. Patow	Clinical Assoc.	LCI NIAID

COOPERATING UNITS (if any)

Lab. of Technical Development, NHLBI; Lab. of Clinical Investigation, NIAID; Neurology Branch, NINCDS; Allergy and Rheumatology Depts., Walter Reed Army Medical Center; MED Pacific, Inc., Seattle, Washington.

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is the development of a clinical, non-invasive monitor of tissue blood flow by analysis of the spectrum of Doppler scattered laser light. The NIH Laser Doppler Blood Flow Monitor has been demonstrated to be highly portable and clinically convenient with sterilizable, rugged flexible 4m fiber optic probes and portable and photodiode detection system. The linearity of the flow analysis processor has been demonstrated in a variety of tissues and clearly resolves physiologic flow changes including instantaneous pulsatile flow in the microcirculation. Muscle blood flow in over 50 patients with neuromuscular disease has been studied and data suggest that post occlusive reactive hyperemia responses may be primary of secondary indicators of disease state. Studies of scleroderma patients' skin blood flow have shown reduction in flow correlates well with disease state. Nasal Blood flow is being assessed as quantitative measure of allergic and drug responses in the nose.

Objectives: Ongoing clinical applications include muscle blood flow at open muscle biopsy in muscular dystrophy patients, skin blood flow in normals and scleroderma patients and potential for therapy assessment, and allergy testing using quantitative skin and nasal blood flow responses. Specific objective at this stage is the application of the instrument and technique in the above variety of clinical and experimental problems. Assistance to the commercial manufacturer (Med Pacific) is being provided under the NIH patent license agreement to insure a high quality commercial instrument.

Methods Employed: The present form of the apparatus has demonstrated its clinical convenience and portability. Minor modifications to probe tip are made for specific applications. Methodologies for clinical diagnosis are developed in collaboration with clinicians. The modifications suggested and implemented in the commercial instrument design are based in spectral noise analysis and theoretical analysis of the method.

Major Findings: (1) The commercial models have been dramatically upgraded to performance comparable to NIH prototype. The mean frequency detection scheme and fiber optic system developed at NIH has been implemented in all commercial devices. (2) A rigorous scattering theory substantiates the validity of our analysis method as do empirical correlations with alternative techniques. The instrument output conversion of 1 volt   15 ml/min/100gm tissue holds with small variations for very different tissue types. (3) Measurements of local muscle blood flow dynamics in patients with neuromuscular diseases indicate abnormalities distinct to different disease types. (4) Scleroderma patients fingertip blood flow appears to fall in three easily-discernable classes asociated with the severity of the disease and a simple measurement protocol may elucidate efficacy of drug therapy. (5) Nasal blood flow has been shown to be sensitive to allergic state and various nasal challenges.

Proposed Course: Cooperate in clinical trials to establish the instrument as a useful clinical and experimental tool.

Significance: The NIH Laser Doppler Blood Flow Monitor is an instrument which holds promise for study of the local tissue microcirculation. It has potential applications in the research laboratory, and in the clinical study of microvascular disease, peripheral vascular disease, allergy testing, screening of vaso-active drugs, and the monitoring of patients with burns and skin grafts.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10113-02 BEI

PERIOD COVERED
October 1, 1982 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Nuclear Magnet Resonance (NMR) Imaging System for Infants

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. I. Hoult	Visiting Scientist	BEIB DRS
OTHERS:	C.-N. Chen	Expert	BEIB DRS
	M.S. Silver	Electronics Engineer	BEIB DRS

COOPERATING UNITS (if any)
NICHD, NCI, CC, NIDR

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Nuclear Magnetic Resonance Imaging

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .35	PROFESSIONAL: 3.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

NMR imaging obtains, non-invasively, the internal distribution of an element (e.g. the protons of water) in an object, and also the distribution of selected physical parameters which are closely related to the environment in which that element reside. Among the many possible ways of obtaining NMR images the preferred technique in this laboratory is the rotating frame method. It has the advantages of avoiding switched or rotating field gradients, and of simplifying the image reconstruction process.

The system under development in BEIB comprises the following components: a spherical electromagnet, a probe, an NMR spectrometer, a PDP 11/34 minicomputer, an array processor, and a display unit. The system is designed for small objects such as premature babies. Except for portions of the probe and of an interface, other hardware and most of the software are ready for producing NMR images.

Objectives: The aim of this project is to explore the various engineering and chemical problems involved in NMR imaging, and to optimize the experimental conditions so that images of the highest quality can be obtained in the shortest time.

Methods Employed

Pulse Programmer

This is the control center of the whole system. It controls the NMR spectrometer, timing, sequencing and data conversion. It can also monitor the field gradients and field frequency lock if so desired. The hardware of this unit is completed. An interface to the computer has been built and is currently under test.

Display Unit

The refresh memory of the Ramtek display unit has been extended from ten bits to twelve bits. Two LAF PROM's have been installed in order to perform some versatile Logical/Arithmetic functions quickly.

Probe

A preamplifier for the probe has been designed and mostly constructed, apart from the insertion of several capacitors which have to meet stringent requirements. These components are under investigation.

Computing

A selective /2 pulse has been worked out numerically. The pulse programmer and a Hewlett-Packard plotter have been interfaced to the PDP11. Several software packages were written for these two units. The pulse programmer can be controlled from its front panel, but will soon be subject to the computer.

Miscellaneous

As a side project, we have used the present setup to do one dimensional imaging. It is a perfect way to study the diffusion profiles of THF in gelatin at low temperature. This is in collaboration with Dr. S. Schein of the dental institute.

Proposed Course: The RF probe and the pulse programmer software will be completed. We expect to get NMR images by rotating frame zeugmatography in the next year. Probes of other geometries and designs will be built in order to explore other NMR imaging methods. Reconstructive methods will be implemented.

Publications

Hoult, D.I., Goldstein, S.R. and Caponiti, J., "An Electromagnet for NMR Imaging", Rev. Sci. Inst. 52, 1342 (1981).

Goldstein, S.R., Hoult, D.I. and Caponiti, J., "Mechanical Design of the NIH Imaging Magnet", Adv. Bioeng. 1981, Am. Soc. Mech. Eng., p. 47, (1981).

Hoult, D.I., Chen, C.-N. and Eden, H.S., "Array Processing - A New Dimension in NMR Computing", J. Mag. Res. 45, 182 (1981).

Hoult, D.I. in "NMR Imaging", Eds. R.L. Witcofski, N. Karstaedt and C.L. Partain, "Radiofrequency Coil Technology in NMR Scanning", Bowman Gray School of Medicine, Winston-Salem, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10114-01 BEI

PERIOD COVERED
October 1, 1981 to Setpember 30, 1982

TITLE OF PROJECT (80 characters or less)

Phasic Aortic Pressure Control System for Awake Dogs

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

P.I.:	S.R. Goldstein	Chief, MES	BEIB DRS
OTHER:	R.Patterson	Senior Investigator	NHLBI CB

COOPERATING UNITS (if any)
Cardiology Branch, NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation Branch

SECTION
Mechanical Engineering Section

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: .6	OTHER: .4

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Control of phasic aortic pressure in experimental dogs is achieved with a feedback pressure control system. The system is designed to either change pressure during several beats in an arbitrary manner, or to reproduce a pressure waveform over an extended period of time. Typical use is for evaluating effects of drug intervention where the pressure waveform before the intervention is reproduced after the intervention, thus allowing changes in inherent muscle contractility to be observed apart from changes in systemic pressure. A modification of the system will be used to control end diastolic filling pressure.

Objective: To control pressure downstream of the heart in experimental dogs so that the variable is either a) changed in an arbitrary manner to assess the effect on ventrical performance, or b) to maintain this variable parameter during other interventions e.g. drugs, so that effects of the intervention are not obscured by change in downstream pressure (and coronary perfusion).

Significance: The circulatory system is extraordinarily complex with a multiplicity of feedback mechanisms which prevent unequivocal interpretation of the effects of various interventions comonly performed in its study. Decoupling of the downstream load pressure (and coronary perfusion pressure) should greatly facilitate the interpretation of drug interventions where at present, drugs that alter contractility also alter systemic pressure. Additionally, the ability to arbitrarily change load pressure should provide a means of validating mathematical models of ventricular function where load pressure is a key parameter. Similarly, control of end diastolic pressure in conjunction with downstream pressure in an intact animal should give the investigator great flexibility in the design of experiments that elucidate the inherent contractile properties of the myocardium.

Proposed Course: An aortic pressure control system has been conceived, analyzed, simulated on a computer, designed, and is presently being debugged during bench testing. After checkout in experiments with the dog, it will be extended to control end diastolic filling pressure.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10115-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Servomechanism for Controlled Motions of Primates

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	S. R. Goldstein	Chief	MES BEIB DRS
OTHERS:	A. Rich		SES BEIB DRS
	F. Miles	Senior Investigator	LSR EI

COOPERATING UNITS (if any).

Laboratory of Sensory Motor Research, NEI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .9	PROFESSIONAL: .4	OTHER: .5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Controlled oscillatory motions of a primate restrained in a special chair are produced by a position control servomechanism. Triangle and sinusoidal wave forms of angular position are produced by a large, geared torque motor controlled by a power amplifier, input, and feedback signals.

Objective: To precisely control the motions of primates (and eventually humans) during tests related to the vestibular ocular reflex.

Significance: The new system provides faster velocities, more precise positioning, and heavier loads (eventually human) than existing equipment.

Proposed Course: A system satisfying all requirements was designed, built, debugged, and delivered.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10116-01 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Modeling of Arterial Pulse Waves

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. S. Chadwick	Biomedical Engineer	BEIB DRS
OTHERS:	D. Goldstein	Senior Investigator	EHL NHLBI

COOPERATING UNITS (if any)

NHLBI - Endocrinology Hypertension Lab

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Mechanical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An analytical model of the arterial circulation is being developed which can reproduce the phasic pressure as measured in normal and hypertensive subjects. Particular emphasis is directed toward an understanding of the genesis of the peripheral dicrotic wave, which has different characteristics in normals and hypertensives.

PHS-6040
(Rev. 2-81)

Methods Employed: A literature review has revealed two distinct approaches to modeling the arterial pulse characteristics: "Windkessel" or elastic reservoir theories, and network analyses of the transmission of pulse waves. An asymptotic analysis of viscous flow in a network of distensible tubes has been undertaken to show when the former approach is a useful approximation to the latter approach. Various hybrid schemes consisting of distensible tubes and elastic reservoirs are also being investigated.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10117-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Optimum Cryoprotectant Introduction/Removal for Blood Components

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. L. Levin	Biomedical Engineer	BEIB DRS
OTHER:	J. Whang	Chemical Engineer	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, Maryland 20205

TOTAL MANYEARS: 0.40	PROFESSIONAL: 0.15	OTHER: 0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The purpose of this project is to study the osmotic behavior of platelets and other blood components during the introduction and removal of cryoprotective agents (CPAs) from both an analytical and an experimental point of view. Comparison of the theoretical predictions of cell behavior during CPA introduction and removal based upon a non steady state mass transfer model with experimental observations of the responses of cells to changes in the composition of their suspending media will hopefully facilitate the development of optimum CPA introduction and removal protocols.

Objectives:

(1) To experimentally observe the osmotic response and functional integrity of platelets and other blood components to the introduction and removal of cryoprotective agents.

(2) To correlate our analytical and experimental findings and deduce the rate-limiting transport parameters.

(3) To develop optimum CPA introduction/removal protocols which can be readily employed in blood banks.

Methods Employed:

(1) Mathematical modeling and data analysis will be accomplished through the use of the American Red Cross' VAX 11/780 computing system and associated computer graphics facility.

(2) Experimental observations will be conducted with the aid of a modified "stop-flow" apparatus.

Significance: High concentrations of cryoprotective agents (CPAs) such as glycerol and dimethylsulfoxide are necessary for the successful cryopreservation of cells, tissues, and organs. Unfortunately, the introduction of CPAs prior to freezing and their removal after thawing has been documented in many instances to be as damaging as the freeze-thaw process itself. In order to help avoid the possible adverse osmotic effects observed by many investigators during CPA introduction and removal, a comprehensive theoretical and experimental analysis is necessary.

Proposed Course: To continue our current theoretical and experimental studies of the responses of platelets to the introduction and removal of cryoprotective agents. To design a modified dialysis system which will be capable of changing the CPA content of platelets and other blood components in a controlled manner.

Collaborator: The experimental aspects of this project are being conducted in the laboratories of Dr. Harold T. Meryman, Chief of the Cryobiology Laboratory of the American Red Cross Blood Research Laboratory, Bethesda, MD.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10118-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Grip Strength Dynamometer for Indiviual Finger Force Measurements

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	D. Markle	Biomedical Engineer	MES BEIB DRS
OTHERS:	J. Ortiz	Biomedical Engineer	CC REHAB
	W. Schneiderwind	Physical Therapist	CC REHAB

COOPERATING UNITS (if any)
Rehabilitation-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Mechanical Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .5	PROFESSIONAL: .5	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A grip strength dynamometer has been developed which measures the magnitude and direction of the forces generated by each finger while gripping the device. The force transducers are rectangular posts instrumented with strain gauges such that two orthogonal forces at right angles to the top of the post and one force normal to the posts' top and measured. The dynamometer is secured in a gymbal mount whose rotational axes are approximately coincident with the wrists. Potentiometers connected at the gymbal's axes measure the angular orientation of the wrist with respect to the forearm. The instrument is used in conjunction with a Tektronix 4052 computer capable of sampling, storing, processing and displaying all the data. The system may be used to evaluate the progress of patients under various rehabilitative protocols, to monitor the progression of various degenerative diseases and possibly as a diagnostic tool.

Objective: To measure the magnitude and direction of the forces generated by each finger while gripping as a means of evaluating patient progress under various rehabilitation protocols.

Methods Employed: For each finger a rectangular post was constructed and instrumented with strain gauges so as to allow independent measurements of two orthogonal force acting at right angles to the top of the post, and one force acting normal to the post's top. The top of the post is equipped with a finger pad mounted on a ball joint such that all forces applied to the post via the finger pad act through the same point. The magnitude and direction of forces applied to the finger pads are calculated by combining the three measured vectors into a single force resultant. The instrument is used in conjunction with a Tektronix 4052 computer capable of sampling, storing, processing and displaying all the data.

Significance: At the present time this is the only system available to measure the magnitude and direction of individual finger forces. Such information is useful to rehabilitation personnel and orthopedists interested in the biomechanics of the hand, evaluating rehabilitative protocols and monitoring patient progress.

Proposed Course: The device is currently being evaluated for use in a variety of clinical studies.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10119-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Optical Multichannel Analyser - Experiment Control

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	H. Cascio	Electronic Engineer	EEES BEIB DRS
OTHERS:	P. Smith	Visiting Scientist	EEES BEIB DRS
	I. Levin	Section Chief	LCP NIADDK
	R. Adams		LCP NIADDK

COOPERATING UNITS (if any)
LCP-NIADDK

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.9	0.1

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A controller has been developed which coordinates the setting of a specific temperature in a sequence and the gathering of ir Raman spectra of biological samples by an optical multichannel analyzer (OMA). The design incorporates a microprocessor which is capable of establishing a certain experimental state and directing the data gathering sequence of the OMA.

Objectives: To provide a mechanism capable of interacting directly with the OMA in a manner providing for control of associated experimental apparatus. In particular, to control the temperature of a sample, to maintain the temperature during the data gathering sequence, and to establish the next, if any, temperature in a programmed sequence.

Methods Employed: The controlling device performs the following tasks. It accepts the necessary temperature sequence consisting of an initial temperature, temperature increment, number of increments, and the equilibration time at each step. A maximum of 50 such sequences can be loaded. Secondly, the controller directs the temperature bath to establish each step of the sequence, and maintain each set temperature until the data gathering sequence is finished. Finally, the controller interacts with the OMA so that while sample temperatures are being established the detector is quiescent but during data gathering the controller relinquishes control to the OMA.

The Pro-Log PLS 858 single card microprocessor has sufficient on card memory, input and output ports, and interrupt inputs to contain the necessary algortihm and to operate the required hardware to satisfy the above tasks. The OMA used in these experiments is a Princeton Applied Research model 1420 intensified diode array, model 1218 controller, and model 1215 console.

The controller measures sample temperature by monitoring the voltage developed across a Keithley DVM by a copper-nickel thermocouple. This voltage is compared to a series of voltage-temperature equivalents stored as a look-up table in memory. Cycling the heater with every reading of the DVM produces a stability of 0.25C for each set temperature. This stability is limited by the number of digits available from the DVM. Interaction between the OMA and the controller is via two lines. The OMA activates the controller by a program keystroke sending a pulse on the BIT 6 line, which sets the detector in a quiescent state and waiting for a pulse on the external event line. The controller provides this pulse at the end of the equilibration period following a set temperature. Other features include a 25C stand-by control, and an alarm system. The latter is enabled if the set temperature exceeds the range -50C to 100C. A connector is available to control power to external devices if this condition exists.

Significance: This design although specific to a single task and experimental situation does not limit its applicability. A similar design can be used for other situations and as such represents an important contribution for the growing number of users of OMA detectors who require external experimental control.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10120-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Vidicon Detection for Fluorescence Microscopy

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Smith	Visiting Scientist	BEIB DRS
OTHERS:	H. Cascio	Electronic Engineer	BEIB DRS
	R. Balaban	Staff Fellow	KE NHLBI

COOPERATING UNITS (if any)
KE-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A vidicon detector has been interfaced to a minicomputer to provide scan control and data gathering. The detector is to be used to monitor spatial localization of metabolic activity in cells by fluorescence microscopy. A composite video output has been obtained from this same detector.

Objectives: To produce a detection system for a fluorescence microscope capable of providing both a normal output suitable for a display monitor and a spatial-wavelength output suitable for determining fluorescent intensity changes as a function of position and time.

Methods Employed: A model 1254B silicon intensified target vidicon detector and a model 1216 controller, both manufactured by Princeton Applied Research, have been interfaced to a Digital Equipment Corporation DECLAB-11/MNC minicomputer. A FORTRAN program has been developed to permit control of the scanning parameters of the vidicon and to collect the output data. The program is interactive and allows for change of parameters with error checking to reduce the possibility of damage to the detector by overscanning a small target area.

The vidicon has been mounted on the fluorescence microscope to permit either normal observation of the image plane or observation of a slit image after passing through a monochromator.

A modification has been made to the vidicon controller and an electronic circit constructed to produce a composite video signal suitable for display monitors or for storage on video tape recorders. The monitor display at present is not symmetric, a problem which must be overcome to produce acceptable displays. The cause is probably a misalignment of the vidicon tube and the deflection yoke. For programmable scanning conditions, the dynamic range of the detector has been improved by increasing the videogain after subtraction of the background signal.

Significance: The ability to switch from a normal composite video signal to a programmed non-standard vidicon scan provides an extra level of sophistication for microscope work. The actual object seen by the vidicon can be observed and aligned to an optimum configuration before switching to the wavelength analysis mode. This is expected to be highly attractive to workers in this field.

Proposed Course: To complete the composite video circuitry and establish a satisfactory image on the monitor display. To analyze the wavelength-position data for accuracy. To provide for time resolved information within the limits of the detector readout time.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10121-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

IEEE-488 General Purpose Interface Bus Program Development

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. R. Clem	Electronic Engineer	EEES BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.2	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Through the use of IEEE-488 General Purpose Interface Bus (GPIB) equipment and inexpensive desktop computers, sophisticated instrumentation and data-acquisition systems can be assembled quickly and inexpensively. The BEIB is continuing to develop the expertise to satisfy requirements where this approach provides the optimum solution. This capability is further assisted by the BEIB-SERP specifying the IEEE-488 interface capability on new equipment acquisitions wherever possible.

Objectives: Continue to develop expertise in the Branch in the use of IEEE-488 GPIB equipment, instruments, and controllers and recommend bus-compatible instruments for acquisitions by the SERP in order to be prepared to respond quickly to a request for an instrumentation system.

Methods Employed: Generally an instrumentation system will be assembled around the IEEE-488 GPIB for one of four reasons: 1) a prototype system is desired to prove feasibility before a dedicated system is designed and built, 2) a temporary system is needed to satisfy an urgent, short term need, such as replacing a dedicated system that is out of operation for maintenance or repair purposes, 3) to expedite data acquisition into a computer system for further analysis, or 4) to produce a system which is inherently flexible enough to adapt to a wide range of potential needs. Systems to solve one or more of these requirements have been produced for Dr. Phil Ross, LMB, NIADDK and Dr. Robert Simpson, LCDB, NIADDK.

Significance: the capability of assembling an instrumentation system with a controller and GPIB-controlled instruments allows the EEES to provide a rapid response to an investigator's call for instrumentation. By assembling a system with "off-the-shelf" instruments from the SERP, the cost of special-purpose measurement or control systems can be kept quite low. If the experiment is a short-term project the instruments can be returned to the SERP with virtually no expenditures, by the investigator, for equipment.

Proposed Course: Continue to maintain state-of-the-art capability in the field of bus-compatible instruments and controllers. Seek to make this capability better known and understood around NIH.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10122-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Mini-Computer Controlled Fermentation System

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	T. R. Clem, Sr.	Electronic Engineer	BEIB DRS
OTHERS:	A. F. LeRoy	Chemical Engineer	BEIB DRS
	Y. Shiloach	Head, Pilot Plant	LCDB, NIADDK

COOPERATING UNITS (if any)
LCDB - NIADDK

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering Section

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 1.5	PROFESSIONAL: 1.0	OTHER: 0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A computer-controlled fermentation system is continuing to be developed for monitoring and controlling the fermentation process. The system operates from a desktop computer functioning as a central controller and a data acquisition device. Various monitoring and control instruments and devices are connected to this computer via the IEEE-488 GPIB. The same system controller and most of the program and external instruments can be scaled to various sizes of vessels with very few changes. Parameters can be selected initially and changed dynamically as desired as the experiment proceeds.

PHS-6040
(Rev. 2-81)

Objectives: Design and implement an instrumentation, data acquisition, and control system to provide monitoring and control of the fermentation process in any of several sizes of fermentation vats. The control function is designed in a way that will allow automatic alteration of control parameters at various points in the fermentation process.

Methods Employed: The system currently in use consists of some instruments which were already in use in the pilot plant and some instruments which were either purchased or designed and built specifically for this project, all connected to an inexpensive desktop computer. The control program is written in BASIC which facilitates understanding and modification by the user. Most of the transducers used are commercial instruments connected to the computer via the IEEE-488 GPIB.

Significance: Computer monitoring and controlling of the fermentation process will produce several significant advantages over the present methods. By using the computer to make decisions based on what is occurring in the fermentation process, parameters can automatically be altered to produce either an increased yield of a desired product or a more pure form of the product. The computer can also perform some of the "housekeeping" tasks associated with running a fermentation process that would normally require an operator.

Proposed Course: To continue expanding and refining the system to provide additional functions, control and monitor additional parameters, and design and implement more sophisticated control programs.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10123-01 BEI

PERIOD COVERED
October 1, 1981 to September 1982

TITLE OF PROJECT (80 characters or less)

Monkey Feed Game

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Wooten	Electronics Engineer	EEES BEIB DRS
OTHER:	M. Morin	Scientist	R VR

COOPERATING UNITS (if any).
RIS, VRB

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .3	PROFESSIONAL: .3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A food delivery system for the individually caged monkeys in the veterinary branch is being developed. The prototype for one cage involves a microprocessor, a lighted touch-activated switch panel, and a universal feeder. These parts configure into an entertainment and reward feeding system for the monkey.

Objectives: The objective is to improve the quality of life of the caged monkeys and provide them with an activity which can also provide them their feedings throughout the entire day.

Method Employed: A microprocessor controls a game which involves the 4 lighted switches of the touch panel. A sequence of lights is displayed on the panel which the monkey can follow by touching the appropriate switches. If the monkey follows the sequences he will be rewarded immediately with a food biscuit which is delivered by the feeder under program control. If the monkey doesn't follow the sequences he will be fed fifteen minutes later and the sequence set up will decrease in difficulty. The game is available to be played at regular half hour intervals. An operator panel is available to make changes in game sequences or changes in time intervals. A printer records the progress of the monkey in his ability to play the game.

Significance: The welfare of the animal population used in many of the NIH Scientists' experiments is important. The monkeys who have to be caged separately have been displaying some behavior problems which stem from the fact that they have nothing to do all day. The game will provide them with a challenge and also will extend their feedings throughout the day.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10124-01 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Automated Test Apparatus and Data Handling System for Patient Electrical Safety Program

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Wooten	Electronics Engineer	EEES BEIB DRS
OTHERS:	H. Cascio	Electronics Engineer	EEES BEIB DRS
	W. Friauf	Section Chief	EEES BEIB DRS
	H. W. Metz	Assistant Branch Chief	SES BEIB DRS
	W. Connoley	Section Chief	CCIS BEIB DRS
	R. Corsey	Electronics Engineer	ACES BEIB DRS
	S. Soroka	Programmer	DMB CR

COOPERATING UNITS (if any)

RIS, DCRT

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Two microprocessor based automatic test sets for checking the safety of electrically operated patient care equipment have been designed and built. Test results are stored on cassette tapes which are compatible with the IBM/370 computer. Through discussions with DCRT, a program has been written to input the data from the tapes and file it and manipulate it to provide better documentation and analysis for the safety program.

Objectives: The objective is to provide an automated test set which can safely and accurately measure the parameters of devices in their operating environment. Also the objective is to facilitate the handling, storage, and presentation of this data so that the safety of the equipment being tested can be better evaluted and statistical and trend analysis of past and present data can be done.

Methods Employed: Using microprocessor technology, manual input and bar code scanner input can be interfaced to the test set to provide identification of the equipment and annotations on the test itself. A tape transport stores all this data on cassettes.

Significance: By monitoring the results from the safety test data, problems in the safety and everyday operation of the equipment can be detected or even predicted to prevent hazards to the patients.

Publications

Wooten, C.K., Corsey, R.: "Microprocessor-Controlled Automated Test Sets". Journal of Clinical Engineering. 7/3, July 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10125-01 BEI

PERIOD COVERED October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Automatic Assessment of Cytochrome P450

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. F. Bonner	Physicist	BEIB DRS
OTHER:	P. Bungay	Chemical Engineer	BEIB DRS
	L. Pohl	Pharmacologist	LCP NHLBI
	R. Branchflower	Staff Fellow	LCP NHLBI

COOPERATING UNITS (if any).

Laboratory of Chemical Pharmacology, NHLBI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .35	PROFESSIONAL: .35	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A continuous flow analyzer has been designed and tested for use wth a programmable dual channel spectrophotometer. The system allows continuous monitoring of a chromatography column output containing cytochrome P450 by comparing the difference spectra at 420, 450, and 490 nm of the reduced form and that reacted with carbon monoxide. The current prototype resolved 10 nanomolar Cytochrome P450 in a resolved measurement volume of 0.8 ml.

Objective: To design and test an automatic instrument for continuously sampling the output of a chromatography column eluting cytochrome P450.

Methods: A continuous flow analyzer was designed using a small volume mixer for adding a reducing buffer to the column elutant and a large area, small volume CO exchanger (silicon rubber diffusion chamber) which allows full reaction of the reduced form with CO. The stream containing the reduced form and that containing the carbomonoxy-form then each flow through separate microflow spectrophotometer cells placed in a microprocessor-based spectrophotometer. The spectrometer is programmed to analyze and print out every 5 sec. the concentration of cytochrome P450 in both active and denatured forms using the difference spectra at 420 nm, 450 nm, and 490 nm. The instrument performance was compared with the existing manual technique.

Major Findings: The system is capable of resolving a peak containing as little as 8 picomoles of cytochrome P450 over a wide range of sample stream flows and any colume flow greater than 0.7 ml/min. The detection threshold is of the order of 10 nM. The pulse broadening results in an independent resolution volume of 0.8 ml. This represents a large increase in resolution over the manual method. Furthermore the instrument is dramatically laborsaving.

Significance: Cytochrome P450 plays an important role in drug interaction, xenobiotic toxicity, carcinogenesis, and regulation and synthesis of a number of endogenous substances. It is suspected that different individuals have different compositions of the family of Cytochrome P450 molecules. The ability to easily monitor these differences afforded by this instrument offers the potential to elucidate further the role this enzyme family plays in pathology and physiology.

Proposed Course: Evaluate the effectiveness of various types of columns (HPLC) to separate minor peaks using the prototype instrument. Determine whether a dedicated instrument would be of significant usefulness; and if so, design and construct one.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10126-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Trace Analysis and Elemental Microanalysis in Biological Materials

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	A. F. LeRoy	Ph.D., Chief	AMS BEIB DRS
OTHERS:	M. Linnoila	M.D., Ph.D., Staff Psychiatrist	CPB NIMH
	W. P. Hagins	M.D., Ph.D.	LCP NIAMDD
	M. Egorin	M.D.	LCB NCI
	L. Zwelling	M.D.	LMP NCI
	P. Galle	Prof. of Biophysics	Medical Faculty, Creteil
	G. Mathe	Director	ICIG, Villejuif, France
	S. Tsai	Ph.D.	LCM NHLBI

COOPERATING UNITS (if any)
CPB-NIMH; LCM-NHLBI; LCP-NIAMDD; LMP-NCI; ICIG-Villejuif, France; Biophysics Department, Medical Faculty of Creteil, University of Paris.

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Analytical Methods

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	4.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Flameless atomic absorption spectrophotometry (FAAS) and neutron activation analysis (NAA) have been used for quantitation of vanadium, platinum, calcium, iron, cobalt and some other elements in biological tissues and fluids. The analyses are important in clinical biochemical, pharmacokinetic, and binding studies. Very sensitive analytical techniques are necessary because, in some instances, the elements are present in trace concentrations (i.e. typically in the part-per-million (10^{-6} g/g) or part-per-billion (PPB) (10^{-9} g/g level and less frequently at the part-per-trillion (PPT) (10^{-12} g/g) level, and, in many cases, the sample size is small as well (i.e. less than 1 ml). Elemental Electron Probe Microanalysis has been performed using a Cameca MBX instrument equipped with a transmission microscope (Creteil, France) to localize several elements, platinum, iron and sulfur on the microscopic scale in different tissues. Separation techniques including ion-exchange chromatography, solvent extraction, and electrophoresis have been used to purify samples, fractionate and concentrate chemical species before analysis, and eliminate substances interfering with trace level assays.

Objectives: The objective of this work is to improve existing analytical and identification techniques for metals and metal complexes in biological materials and develop new ones. Detection limits of the order of picograms to nanograms in milligram samples and simplified sample preparation have been sought. Quantitation of vanadium, platinum, calcium, cobalt, and iron has been emphasized; other elements of biological signficance are worked with as interest develops. Localization of elements on the microscopic scale has been performed on biological tissues of interest.

Methods Employed: Quantitative elemental analysis is being performed principally by flameless atomic absorption spectrophotometry. Control of temperatures generated in a graphite furnace as a function of time permits analysis even when considerable molecular and broad-band absorption occurs during combustion. Neutron activation analysis is being used to perform referee analyses and analysis of samples ill-suited to FAAS. Electron probe microanalysis has been used to identify the presence of specific elements in subcellular structures.

Ion exchange chromatography and electrophoresis have been used to fractionate samples of body fluids, with subsequent quantitation of metals in the fractions. With these techniques, improved resolution and analytical sensitivity are expected to permit findings of biological significance.

Major Findings: Vanadium levels in samples of blood plasma or CSF from patients can be measured quantitatively in the low PPB range even in samples of small volume ($\sim 20\ \mu l$). The sensitivity of the technique for Vanadium is approximately 15×10^{-12}g. These concentrations are being correlated with affective behavior in patients with manic-depressive syndrome. Tubular lesions characterized by highly developed coalesced lysosomal structures develop in the kidneys of rats treated with repeated doses of CDDP an important chemotherapeutic agent for treatment of certain cancers. These lysosomes contain electron-dense granules not observed in controls. The dense granules contain platinum and large amounts of iron and sulfur not found in the controls. Quantitation of these elements is underway.

Significance: Quantitation, identification, and characterization of metal species at trace levels in biological tissue samples, often very small, are important in biochemical research and environmental toxicology. Quantitation of a specific element in tissues and body fluids can aid understanding of drug action and other biochemical processes. Methods being developed offer quantitation of stable elements and obviate the need for radiolabeled substances in many instances.

The ability to quantitate Vanadium at trace levels in body fluids is important in obtaining objective data in studies of major affective disorders and on the inhibition of enzyme activity and its postulated link with these disorders. Assimilation of iron in the kidney of CDDP treated animals may be involved with the renal toxicity observed.

Proposed Course: Extend applicability of FAAS to include more tissue types. Try to minimize or eliminate pretreatment required. Complete analyses for localization of the platinum and iron in renal tissues. Perform necessary analyses for elements using neutron activation to confirm flameless atomic absorption spectrophotometry results. Expand use of chromatography and solvent extraction to purify samples and fractionate and concentrate chemical species under study. Undertake studies to reduce iron assimilation in kidneys of treated animals and determine its effect on toxicity. Continue work in vanadium determinations and develop techniques for speciation of the vanadium.

Publications

Berry, J.P., Brille, P., LeRoy, A., Gouveia, Y., Ribaud, P., Galle, P. and Mathe, G. Experimental Ultrastructural and X-ray Microanalysis Study of Cis-DDP in the Rat: Intracellular Localization of Platinum. Cancer Treatment Reports 66, 1529-1533 (1982).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10127-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Oxygen Equilibrium Curve Appartus

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Gibson	Electrical Engineer	EEES BEIB DRS
OTHERS:	R. Berger	Physicist	LTD NHLBI
	C. Townsend	Student	LTD NHLBI

COOPERATING UNITS (if any)
LTD-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.2	.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A microprocessor based instrument has been constructed to produce an oxygen equilibrium curve on whole human blood semi-automatically. The apparatus consists of a reaction cell with PO_2 and PCO_2 electrodes, an electrometer, and a microprocessor to do the calculations. All the programs are written in FORTRAN and the system is designed as a research tool. Therefore, almost all parameters are changeable. The apparatus is now in the testing phase.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10128-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
4 Channel Programmable Integrated Unit for Data Acquisition On Electron Microscope

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Gibson	Electronics Engineer	BEIB DRS
OTHERS:	C. Fiori	Physicist	BEIB DRS
	R. Leapman	Visiting Scientist	BEIB DRS
	K. Gorlen	Electronics Engineer	CSL DCRT

COOPERATING UNITS (if any)
CSL-DCRT

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: .5	PROFESSIONAL: .3	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Due to poor counting statistics, the bright field, dark field and energy loss signals must be averaged over time. This is done by integrating the signals simultaneously at each pixel of the image. The programmable integrators have programmable gain and programmable time constants to enable the researcher to use as much of the dynamic range of the analog to digital converter as possible.

PHS-6040
(Rev. 2-81)

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10129-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Descanning Electron Beam for Energy Loss Analysis in Electron Microscope

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI's:	C. Gibson	Electronics Engineer	BEIB DRS
	R. Ornberg	Visiting Scientist	LNNS NINCDS

COOPERATING UNITS (if any).

LNNS-NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.3	.2	.1

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

To prevent severe damage to biological samples during energy loss analysis it is necessary to scan the electron beam over the sample in a scanning transmission electron microscope. However, if the beam is scanned over the sample, the beam is also scanned over the entrance of the energy loss analyzer which produces unusable results. Therefore, a circuit has been built which descans the beam after it has passed through the sampel and keeps the beam stationary at the entrance of the energy loss analyzer from magnifications of 1000 to 100,000.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10130-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Dual Differential Thermal Titration Apparatus

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Gibson	Electronics Engineer	BEIB DRS
OTHER:	R. Berger	Physicist	LTD NHLBI

COOPERATING UNITS (if any)
LTD-NHLBI

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 3.5	PROFESSIONAL: 1.0	OTHER: 2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

A microprocessor based semi-automatic data collection and correction unit has been built to measure both pH shifts and heats of reactions using a dual differential measurement cell which contains fast thermistors, fast pH electrodes, and is temperature stabilized.

The data is collected with a 16 bit A/D converter and is displayed and plotted in real time. The data is then stored on disk, a separate program corrects the data for heat losses using finite element techniques. During data collection, the processor controlls a syringe drive to deliver the reactants.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10131-01 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Instrumentation for Chromaffin Granule Intensity Fluctuations

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. Gibson	Electronic Engineer	BEIB DRS
OTHERS:	P. Smith	Visiting Scientist	BEIB DRS
	S. Morris	Expert Consultant	NTS NINCDS

COOPERATING UNITS (if any)

NTS-NINCDS

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electrical and Electronic Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Chromaffin granules aggregate with subsequent release of stored cell components. Scattering and fluroescent intensity changes, associated with probes embedded in the membrane, are used to study the rate of granule aggregation. Stopped flow instrumentation is used to initiate the process and a multichannel data gathering system has been developed to record the data. A data link to the DEC 10 computer has been established.

PHS-6040
(Rev. 2-81)

Objectives: To provide the instrumentation and data gathering system to record the scattering and fluorescent intensty changes. To store the data in a format compatible with existing analysis programs.

Methods Employed: An Aminco-Morrow stopped-flow apparatus was used to mix the labelled granules. Illumination was provided at 455 nm (an absorption minimum for rhodamine) to excite granules containing NBD which transfers energy to rhodamine on aggregation. Fluorescent changes at 580 nm (rhodamine fluroescence) were monitored perpendicular to the excitation path, and simultaneous intensity changes, due to aggregation, of the excitation light were also measured.

Date is collected on an MDS-800 Microcomputer System using a User Friendly Interactive Program. All programs are written in FORTRAN and data is stored on a floppy disc. The program displays data on a storage CRT in real time and utilized a dual time base. A separte program is used for transferring data to the DEC-10 in DCRT for analysis.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10132-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Image Processing and Cell Classification

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. R. Ellis	Expert	BEIB DRS
OTHER:	B. H. Smith	Assistant Chief	SNB NINCDS
	A. L. Robinson		SNB NINCDS
	M. A. Greenwood		SNB NINCDS
	C. C. Gibson	Electronics Engineer	BEIB DRS
	V. J. Sank	Expert	SNB NINCDS

COOPERATING UNITS (if any)
SNB-NINCDS

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.5	PROFESSIONAL: 0.25	OTHER: 0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

In vivo cell culture is an effective method for the study of the effects of chemotherapeutic agents on neurological tumors. Quantitation of all but the most rudimentary of these effects is generally beyond the ability of human observers. Thus, an automated system for acquisition of image data, extraction of parameters, and statistical processing of results is necessary for any quantitative effectiveness.

Objectives: Quantitative analysis of morphological properties of in vivo Glioma cell cultures under varied conditions and courses of treatment.

Methods Employed: Cell lines are taken from surgical biopsies and cultured by standard methods. Sample cultures are subjected to selected chemotherapeutic procedures. Light microscopic and electron microscopic images of both untreated and treated cell lines are analyzed by a Bausch and Lomb Omnicon Feature Analysis System.

This system derives measurements consisting of several parameters -- including area, perimeter, length, breadth, etc. -- and algebraic combinations of them derived from thresholded images. Special purpose hardware and software operates under the control of a Data General Nova 3 general purpose computer and its standard RDOS operating system. Data acquisition and analysis is user controlled through a BASIC language interface for the light microscope system, and through a "FORTRAN Package" of programs for the Scanning Electron Microscope interface.

Major Findings: (1) The overall system has been made to work in spite of the hardware and software support provided by Bausch and Lomb. Determination of chemotherapeutic cytotoxicity using light microscopy of titer plates has been made a reliable production operation with correct statistics. Throughput with human counting and processing was typically from 6 to 8 plates a day, followed by another day for statistical analysis. This has been increased to a range of 3 to 6 plates an hour with statistics and plots done. (2) It has been found that cell culture personnel will alter their plating techniques to match the counting techniques available. Specifically, when automated cell counting is assumed to be available, many more cells are plated in each titer plate well. The counting statistics are then substantially improved and the experiments become much more significant in a statistical sense. (3) We have managed to determine appropriate usage of the FORTRAN Package in spite of absolutely NO documentation from the manufacturer!!

Significance: Reliable, consistent, quantitative processing of image data concerning neurological tumors must be done by machine. The history of operator fatigue and boredom in these tasks is well known. Further, humans can seldom make any quantitative measurements beyond cell counts. This measurement capability can increase the range of feasible investigations by ten to a hundred times.

Proposed Course: Light microscopic analysis of titer plates will continue as a production operation. Electron microscopy will be brought on-line as experience is gained by surgical neurology Branch personnel.

C. C. Gibson is heading an effort to upgrade the machine to make time-sharing possible and to make multi-level imaging a reality. Time-sharing will increase the overall efficiency of the operation by at least 10-fold. Multi-bit images will bring the capabilities of the system more in line with what SNB personnel had in mind when the system was purchased.

Publications

Smith, B. H., J.R. Ellis, A. Robinson, M. A. Greenwood, E. R. Pleasants, C. Cooke, and P. L. Kornblith. "Electron Microscopic Image Processing in the Classification and Quantitation of Human Glial Tumor Cell Properties", EMSA, Washington, DC, August, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10133-01 BFI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Automated Scanning Electron Beam Microanalysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. E. Fiori	Physical Scientist	BEIB DRS
OTHERS:	C. R. Swyt	Physical Scientist	BEIB DRS
	G. Hook	Staff Fellow	BEIB DRS
	R. J. Elin	Chief	CP CC
	R. Dedrick	Chief, ChES	BEIB DRS
	G. Merril	Biochemist	L GCB NMH

COOPERATING UNITS (if any)
CP-CC, L-GCB-NMH

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electron Beam Imaging & Microspectrscopy

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.0	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

During this reporting period the Cameca Electron probe has been extensively modified to enhance its ability to perform biological microanalysis. Solid state backscattered electron detectors have been installed on the objective lens pole piece. These detectors permit the observation of biologically interesting elements, greater in atomic number than 11 from specimens. An energy dispersive x-ray detector and associated computer controlled multichannel analyzer have also been installed. This x-ray detector permits the observation and quantification of elements over most of the periodic table ($Z > 9$). Finally, the existing wavelength dispersive x-ray detectors have been automated and data acquisition can be accomplished using our laboratory PDP 11-60 minicomputer.

A substantial collaborative effort is underway with the clinical pathology branch in the Clinical Center. The work involves the quantification of the magnesium content of individual lymphocytes. Various specimen preparation techniques have been evaluated as well as the mathematical procedures which will be used for the quantification. This work is part of a larger study to provide a quick screening method for the condition of the human cardiovascular system.

Objectives: To provide a capability of performing elemental microanalysis on both bulk and thin biological specimens utilizing focussed electron beam induced X-ray spectroscopy.

Methods Employed: A focussed 2-50 keV electron beam is utilized to ionize microvolumes (containing as little as 10^{-18} grams of matter) of biological specimens. By performing x-ray spectroscopy utilizing Bragg angle x-ray spectrometers and an energy dispersive detector, on the X-rays leaving the ionized volume of the specimen, it is possible to perform elemental microanalysis.

Significance: Electron beam microanalysis permits the solution of certain biological problems which would be difficult, or impossible, by other means.

Proposed Course: To apply the technique to biological research and to study in detail the problems involved in this application.

Publications

Fiori, C. E. and Blackburn, D. B.: "Low Z Glass Standards for Biological X-ray Microanalysis", J. Microsc., Vol. 125, Sept. 1982.

Fiori, C. E., Swyt, C. R. and Ellis, J. R.: "The Theoretical Characteristic to Continuum Ratio in Energy Dispersive Analysis in the Analytical Electron Microscope", Microbeam Analysis, ed. K.F.J. Heinrich, San Francisco Press, 1982

Goldstein, J.I., Newbury, D. E., Joy, D. C., Fiori, C. E., Echlin, P. and Lifshin, E.: Scanning Electron Microscopy and X-ray Microanalysis: A Text for Biological, Geological and Materials Scientists. Plenum Press, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10134-01 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Biological Applications of Analytical Electron Microscopy and Computer Controlled Imaging

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. D. Leapman	Visiting Scientist	BEIB DRS
OTHERS:	C. E. Fiori	Physical Scientist	BEIB DRS
	C. R. Swyt	Physicist	BEIB DRS
	K. E. Gorlen	Electronics Engineer	CSL DCRT
	C. C. Gibson	Electronics Engineer	BEIB DRS
	L. K. Barden	Electronics Engineer	CSL DCRT
	J. S. Delpriore	Electronics Engineer	CSL DCRT
	P. S. Plexico	Chief	CSL DCRT
	R. L. Ornberg	Staff Fellow	SFN NINCDS
	T. Reese	Chief	SFN NINCDS
	M. Henkart	Research Biologist	IB NCI
	K. Kommit	Technician	BEIB DRS

COOPERATING UNITS (if any)

CSL-DCRT, SFN-NINCDS, IB-NCI

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Electron Beam Imaging and Microspectroscopy

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.0	3.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The 200 keV Hitachi analytical TEM-STEM is now being applied to a number of problems in biology. The interfacing of the PDP 11/60 computer to the electron microscope has been completed. This enables computer control of data acquisition, including collection of digitized images with bright-field and dark-field current signals as well as pulse counted energy loss and x-ray signals. A satellite computer controls the electron energy loss spectrometer and the x-ray beam deflectors at a rapid rate. Preliminary energy loss and bright field images have been recorded from test samples including thin sections containing calcium. The results demonstrate the feasibility of 128 x 128 pixel elemental mapping at about 30nm resolution using characteristic energy loss edges. The advantages of displaying chemical information combined with morphological information in a composite image has been demonstrated.

Several samples have also been probed in the point spectrum mode (energy loss and x-ray) to search for a number of elements. We have located calcium in the secretory granules of ameloblasts and fluorine in labelled biological molecules. Computer control of the spectrometers makes more precise and sensitive measurements possible.

Objectives: To use electron energy loss and x-ray microanalysis to probe biological samples and to investigate how elemental imaging can be used to obtain information about cells.

Experimental Techniques: A 200 keV transmission electron microscope with scanning capability combined with an electron energy loss spectrometer and energy dispersive x-ray spectrometer is used to probe thin biological samples. A DEC PDP 11/60 computer has been interfaced to this instrument to produce digitized images which contain morphological and chemical information.

Significance: Analytical electron microscopy is capable of obtaining elemental information on a scale of 10-50 nm in a biological sample. EELS offers a unique method for probing the important light elements on this scale. This is the first time a digitized energy loss image has been obtained under computer control where the spectral background is correctly subtracted at each pixel.

Proposed Course: To collect a series of energy loss images from thin sections to yield the distribution of elements such as calcium and fluorine in cells. The possibility of obtaining information about the nitrogen and oxygen distribution will also be investigated. X-ray maps as well as bright-field and dark-field images will be recorded to give additional information. Work will continue in the point spectrum mode when the concentration of an element is too low to detect in the image.

Publications

R. D. Leapman, L. A. Grunes and P. L. Fejes, "A Study of the L_{23} Edges in the 3d Transition Metals and their Oxides by Electron Energy Loss Spectroscopy with Comparisons to Theory", Phys. Rev. B, 26, 615 (1982).

L. A. Grunes, R. D. Leapman, C. N. Wilkes, R. Hoffmann and A. B. Kunz, "Oxygen K Near Edge Fine Structure: an Electron Energy Loss Investigation with Comparisons to New Theory for Selected 3d Transition Metal Oxides", Phys. Rev. B (1982) 25, 7157-7173

R. D. Leapman, "EXELFS Spectroscopy of Amorphous Material", Proc. Microbeam and Analysis Society, San Francisco Press, p.111 (1982).

C. R. Swyt and R. D. Leapman, "Plural Scattering in EELS Microanalysis", SEM/1982, O. Johori Ed., SEM Inc. Chicago (in press) (1982).

R. D. Leapman, "Applications of Electron Energy Loss Spectroscopy in Biology: Detection of Calcium and Fluorine", Proc. 40th Annual EMSA Conference, Baton Rouge, Bailey(Ed.), p.412 (1982).

R. D. Leapman, "Electron Energy Loss Microspectroscopy and the Characterization of Solids", Asilomar, SEM Inc. Chicago (in press) (1982).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10135-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
The Effects of Fluid Shear Forces on Cultured Endothelial Cells

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. J. Lutz	Chemical Engineer	BEIB DRS
OTHERS:	A. R. Koslow	Research Fellow	American Red Cross
	S. Hilbert	Pathologist	FDA

COOPERATING UNITS (if any)
American Red Cross, FDA-MDB

LAB/BRANCH
Biomedical Engineering and Instrumentation

TION
Chemical Engineering Section

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 2.5	PROFESSIONAL: 2.0	OTHER: .5

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☒ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Arterial endothelial cells in vivo are continuously subjected to varying degrees of shear.stress. These forces have direct effects on the morphology and physiology of the cells and have been implicated as an important factor in atherogenesis. We are designing a simple system for studying the relationship between shear forces and endothelial cell alteration. The system consists of a parallel plate flow chamber which accomodates Thermanox circular cover slips upon which bovine or human umbilical cord endothelial cells are cultured. The flow patterns and shear within the chamber are being characterized using electrochemical shear measurements, flow visualization techniques, and laser doppler anemometry. The design permits studies at shear stresses up to 30 dynes/cm^2 for periods up to 2 weeks. The cell morphology and ultrastructure are being studied by SEM and TEM. The system is versatile and provides the means for biochemical assays, pulsatile flow, and time lapse photography.

PHS-6040
(Rev. 2-81)

Objectives: The objectives of this study are to design and fully characterize a special flow chamber in which arterial endothelial cells can be cultured and can also be exposed to varying fluid shear stresses. When subjected to these fluid shear stresses, the cultured endothelial cells will be studied for changes in their morphology and ultrastructure, and measurements will be made of certain biochemical factors, such as von Willebrand factor, and Factor VIII, as a function of shear stress. It is hoped that we can relate changes in endothelial cell ultrastructure and biochemistry to atherogenesis.

Methods Employed: A flow chamber has been designed and prototypes have been constructed and tested. The chamber consists of a parallel plate arrangement of plexiglass plates approximately four inches wide and ten inches long spearated by a thin (.08 cm) silicon gasket. The gasket is cut out so that it forms a 16° diverging section leading to a parallel section where two circular Thermanox cover silps are positioned flush with the inner surface of the bottom parallel plate. The endothelial cells grow in monolayer on the cover slips. Variable fluid shear stresses are exerted on the endothelial cells by the regulated flow rate of nutrient media through the chamber. The cover slips can be removed from the flow system at various time intervals for examination of the endothelial cells for ultrastructure changes by TEM and SEM. Biochemical assays can be performed on samples of withdrawn media at various times to look for von Willebrand's factor and Factor VIII that has been produced by the cells in response to the shear stress. Immunoassays will be used to measure these factors.

Major Findings: The flow in the test chamber remains laminar throughout the range of desirable flow rates in the experiments. The electrochemical shear measurements agree with theoretical estimates within 10%. Shear stresses up to 30 dynes/cm^2 can be maintained on viable cells for up to 2 weeks with sterile nutrient media. Preliminary studies have demonstrated a reorientation of cells along the direction of flow with an elongation of the cell axis. Cell ultrastructure, as seen by SEM and TEM, shows distinct changes when subjected to shear stresses of 10 to 20 dynes/cm^2

Significance: One theory of atherosclerosis holds that the disease progresses from endothelial cell damage through a series of steps to an atheroma. To understand atherogenesis, it is necessary to identify the initial processes and to develop means of measuring the effects of drugs, blood components, and flow on the endothelial lining. Endothelial insult may change the properties of the endothelium to promote atherogenesis. The advent of improved methods for culturing endothelial cells affords a unique opportunity to study these cells under controlled conditions of chemical environment and flow in the newly designed flow chamber.

Publication

Lutz, R. J., Menawat, A., Peterson, J. I., "A Polarographic Technique for the Determination of Effective Surface Area of Electrodes", accepted for publication, AIChE Journal.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10136-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)
Imaging in Positron-Emission Tomography

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. R. Ellis	Expert	BEIB DRS
OTHERS:	R. M. Kessler		NM CC
	M. Eden	Chief	BEIB DRS

COOPERATING UNITS (if any)
NM-CC

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Office of the Chief

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Positron-Emission tomography (PET) offers unprecedented opportunities to visualize and measure in-vivo organ metabolism. Our current interest centers on the brain, perhaps the least accessible region of the body to non-invasive diagnostic probes.

Meaningful quantitation of the excitation from the computed information requires an accurate and usuable model of the system.

Objectives: (1) Find a good model for the system excitation-response function. (2) Determine limits of diagnostic performance of PET systems from their imaging parameters. (3) Develop a good model for geometrical description of significant regions of the brain.

Methods Employed: (1) Measurements of system response to Positron Emitting Phantoms. (2) Mathematical analysis of models. The point spread function is modelled as a normalized Gaussian with full width at half maximum as a parameter. (3) Computation of values associated with the analysis and phantom parameters. (4) Comparison of the computed values with measurements. (5) Prediction of system response from models, especially image parameters expected for particular brain structures.

Major Findings: The PET System response is generally accepted to be a Gaussian. An analytical solution was found for spherical regions of a three-dimensional Gaussian point spread function, both on- and off-center.

This Gaussian model has been found to match phantom measurements made by Dr. R. Kessler on the Nuclear Medicine ECAT machine very well. The solution has also been found to match several well known "rules of thumb" for PET system performances well.

An existing manuscript describing the phantom results was expanded to include the analytical results and comparisons between experiment and theory.

Significance: The accepted model can be used for detailed calculation and prediction with minimal computation load. Phantom results can be generalized and compared much more effectively than previously thought.

Proposed Course: We plan to use existing results to evaluate the capabilities of existing and proposed systems to image selected combination of physiological and functional structures.

A three-dimensional model of brain structure has been proposed to make more robust use of information from sets of tomographic slices.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10137-01 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Processing of Electron Microscope Images

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	J. R. Ellis	BEIB DRS
OTHERS:	C. E. Fiori	BEIB DRS
	R. D. Leapman	BEIB DRS
	C. R. Swyt	BEIB DRS
	L. K. Barden	CSL DCRT
	K. E. Gorlen	CSL DCRT
	J. DelPriore	CSL DCRT
	C. C. Gibson	BEIB DRS
	K. Kommit	BEIB DRS
	T. Pun	BEIB DRS

COOPERATING UNITS (if any)

CSL-DCRT

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

INSTITUTE AND LOCATION

TOTAL MANYEARS: 3.0	PROFESSIONAL: 2.8	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Electron microscopy is a tool of virtually unlimited potential for chemical geometric analysis of very small samples. Realization of this potential has generally been limited by hardware and software facilities.

The BEIB/DRS-CSL/DCRT Electron Microscope Facility has been designed to overcome most, if not all, of the difficulties and inconveniences associated with data acquisition, processing, storage, and display that have individually or collectively set limits on feasible biological investigations.

PHS-6040
(Rev. 2-81)

Objectives: (1) To provide images which satisfy the knowledgeable observer's basic criteria for credible imagery in a given situation. (2) To allow image data manipulation that will enhance data without forcing an interpretation on it. (3) To quantify the image data and element composition maps in meaningful and robust ways. Such quantification includes error analysis. (4) To make operation of the entire system sufficiently easy that new ideas can be tried rather than dropped for lack of facility to implement them.

Methods Employed: Data acquisition is covered by other reports on this project. Data storage is generally digital, with multi-bit image elements stored on magnetic disk or tape. Display is by a DeAnza Systems IP5500 Color Monitor from a (3 x 8 + 4) bit 512 x 512 data memory.

There is a considerable body of knowledge about human psychophysical responses to images. Several of these principles can be applied to presentation of accurate imagery for a given microscopic situation. Implementation of these ideas has been and will continue to be via software, using either FORTRAN or PASCAL operating under RSX-11M.

Major Findings: Error bounds of peak-to-background ratios for normalized Poisson spectra have been derived.

Programs for overlaying and interpolating signals of different types and of different lattice spacings have been written, debugged and installed for use in the facility. The existing structure of hardware and software built up by this project has been found to be of very high quality.

Significance: This facility can transform the entire field of electron beam imaging. The ability to perform digital processing on multibit images taken simultaneously from a sample and to display the results digitally in color is new. It allows investigations of microstructure and other interrelationships that were previously limited to speculation.

Proposed Course: Appropriate image display and quantitation methods will be selected by interaction with other investigators working with the project. A great deal of software will probably be written in PASCAL.

Publications

C. E. Fiori, C. R. Swyt, and J. R. Ellis. "The Theoretical Characteristic to Continuum Ratio in Energy Dispersive Analysis in the Analytical Electron Microscope", Joint EMSA-MAS Meeting, August, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10138-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Detection and Mass Loss of Fluorine in Labelled Neuro-transmitters

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. D. Leapman	visiting Scientist	BEIB DRS
OTHERS.	C. E. Fiori	Physical Scientist	BEIB DRS
	C. R. Swyt	Physicist	BEIB DRS
	R. L. Kirk	Chemist	LC NIADDKD
	C. R. Creveling	Chief	LBC NIADDKD

COOPERATING UNITS (if any)
LC-NIADDKD, LBC-NIADDKD

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electron Beam Imaging and Microspectroscopy

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Electron energy loss measurements have been made on a series of fluorine labelled biological molecules which were coated onto thin carbon substrates. The fluorine K edge as well as the carbon, nitrogen and oxygen K edges were measured as a function of electron dose in order to establish the rate of mass loss of fluorine. This was done by scanning the incident electron probe over a well defined area while recording the beam current using a Faraday cup. Some of the compounds investigated are closely related to neurotransmitters and it was established that these could withstand a dose of several thousand electrons per Å^2.

Objectives: To estimate the detectability of fluorine in labelled compounds to determine the susceptibility to radiation damage by mass loss.

Experimental Techniques: An analytical electron microscope combined with an electron spectrometer is used to obtain energy loss spectra near the K edge of fluorine while the beam is scanned across the sample.

Significance: The possibility of carrying out elemental fluorine mapping of labelled biological compounds inside cells.

Proposed Course: It is intended to evaluate the technique, first by testing the stability of the compounds under the beam and secondly by attempting to detect them inside cells.

Publications

R. D. Leapman, "Applications of Electron Energy Loss Spectroscopy in Biology: Detection of Calcium and Fluorine", Proc. 40th Annual EMSA Conference, Baton Rouge, Bailey (Ed.), p. 412 (1982).

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10139-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Role of the Secretory Ameloblast in Enamel Mineralization

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	R. D. Leapman	Visiting Scientist	BEIB DRS
OTHERS:	C. E. Fiori	Physical Scientist	BEIB DRS
	C. R. Swyt	Physicist	BEIB DRS
	A. Zaki	Prof. of Dentistry	Dental Inst./Univ. of Ill.
	S. Ashrafi	Prof. of Dentistry	Dental Inst./Univ. of Ill.

COOPERATING UNITS (if any)
Dental Institute, University of Illinois

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electron Beam Imaging and Microspectroscopy

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.2	PROFESSIONAL: 0.2	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Electron energy loss spectroscopy and x-ray microanalysis have been used to study the elemental composition in sections of rat ameloblasts (enamel-forming cells). Calcium has been found in the secretory granules near the Tomes' processes in cells treated with potassium pyroantimonate (a precipitation agent). The immature enamel has also been investigated to estimate the fraction of protein matrix that is present. Preliminary results have been obtained showing elemental energy loss maps of the calcium concentration.

Objectives: To understand the distribution of calcium in the secretory ameloblast and to investigate how this varies when cells are treated with enamel mineralization inhibitors.

Experimental Techniques: An analytical electron microscopy combined with electron energy loss and x-ray energy dispersive spectrometers is used to obtain elemental information from microtomed sections of cells.

Significance: Tooth enamel mineralization depends on an influx of calcium and phosphorus into a protein matrix. The role of the ameloblasts in controlling the influx is not fully understood and analytical electron microscopy might provide significant information about this process.

Proposed Course: To obtain energy loss images of calcium from ameloblasts in order to measure the relative amounts of calcium in different organells, such as the Golgi apparatus and is the mitochrondrion as well as in the intercellular regions, in cells treated with enamel inhibitors and in untreated cells.

Publications

R. D. Leapman, "Applications of Electron Energy Loss Spectroscopy in Biology: Detection of Calcium and Fluorine". Proc. 40th Annual EMSA Conference, Baton Rouge, Bailey (Ed.), p. 412, 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10140-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Energy Loss Software for Biological Microanalysis

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	C. R. Swyt	Physicist	BEIB DRS
OTHER:	R. D. Leapman	Visiting Scientist	BEIB DRS

COOPERATING UNITS (if any)

LAB/BRANCH

SECTION

Electron Beam Imaging and Microspectroscopy

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Software for quantitating electron energy loss spectra has been developed. A deconvolution program which uses Fourier transforms has been written to run on the PDP 11/60 computer. This calculates the single-scattering spectrum from the measured spectrum in thicker samples where plural inelastic scattering is important. An improvement in the accuracy and sensitivity of elemental detection has be found. The algorithm has been tested on some spectra from sections up to 3000 Å thick.

Significance: One of the major limitations of EELS is that due to the plural inelastic scattering in thicker samples. This tends to smear out the characteristic core edges and increase the spectral background. The deconvolution method removes these effects, though some increase of noise is inevitable.

Proposed Course: It is intended to use the deconvolution software wherever possible to optimize the detection limits and accuracy of microanalysis.

Publications

C. R. Swyt and R. D. Leapman, "Plural Scattering in EELS Microanalysis," SEM/1982, O. Johari Ed., SEM Inc., Chicago (in press) 1982.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10141-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Anisotropy of Membrane Probe Molecules.

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

PI:	P. Smith	Visiting Scientist	BEIB DRS
	M. Gottlieb		LPB NIADDK
OTHERS:	R. Bonner	Biophysicist	BEIB DRS
	T. Clem	Electronic Engineer	BEIB DRS

COOPERATING UNITS (if any)
LPB-NIADDK

LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

The anisotropy of probe molecules, embedded in a membrane, following polarized excitation has been studied using the techniques of ground state depletion of the absorption signal and of phosphorescent emission. Phosphorescent emission has been found to be the more sensitive technique. Photomultiplier switching circuits are being incorporated into the detection circuits to reduce the artefacts associated with the laser excitation.

Objectives: To provide instrumentation suitable for measuring the rotation of probe molecules embedded in membranes.

Methods Employed: A Phase-R liquid dye laser, model DL2100, is used to provide polarized excitation at 530nm of erythrosin and eosin probe molecules.

In ground state depletion of the absorption signal, the change in transmission of a low level tungsten light source was monitored for two polarisations parallel and perpendicular to the laser excitation. A major limitation of this technique is that a small signal change is to be detected on a large constant signal. This results in an extremely poor signal to noise and the technique was dropped in favour of phosphorescent emission.

Phosphorescence has the advantage that the signal detected is totally of interest. The two photomultipliers, EMI type 32 , have a switching circuit incorporated to lower the gain by 4 orders of magnitude during the laser pulse which is 1us long. The current window of this reduced gain is 50us. Discrimination between the two orthogonal polarized emissions is provided by a cube beamsplitter.

Proposed Course: To apply the developed instrumentation to the study of polarized emission from eosin and erythrosin probes embedded in red cell ghosts.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10142-01 BEI

PERIOD COVERED
October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Thermal Emitters for Infra-red Camera Calibration

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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OTHERS:	P. Smith	Visiting Scientist	BEIB DRS
	W. Kaye		LCS NIMH
	D. Goldman		LGCB NIMH

COOPERATING UNITS (if any)
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LAB/BRANCH
Biomedical Engineering and Instrumentation

SECTION
Electrical and Electronic Engineering

INSTITUTE AND LOCATION
National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.3	PROFESSIONAL: 0.3	OTHER:

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

An infra-red camera is used to measure the metabolic activity in the brown fat deposits of anorexic and bulimic patients. In order to ensure reliable and reproducible operation, an array of five thermal emitters has been provided at a series of calibration points for each record. This enables the camera's video gain and offset to be adjusted permitting a direct comparison of each record.

Objectives: To provide a reliable method of standardizing the data sets, taken at different times, of the metabolic activity associated with the brown fat deposits of anorexic patients. To calibrate each record with a series of 5 set temperatures allowing the video signal to be adjusted to a preset condition.

Methods Employed: An Inframetrics infra-red camera is used to measure the heat output from various skin surface regions of anorexic patients. The infra-red camera output is displayed using a display monitor using a composite video signal. Photographic records taken of the data are digitized and subsequently analyzed on an image processor for variation of heat production from specific areas. Calibration of the records was initially performed by normalizing the video signal to midrange for the carotid artery temperature.

A more suitable method of calibrating the records is to provide fixed thermal sources at a range of temperatures centered around the median temperature to be scanned. The camera can then be adjusted to the same setting on each occasion and, further, each individual record contains the calibration information.

Proposed Course: The series of calibration points will be evaluated for stability and reliability. If these prove to be acceptable, the unit will become a standard feature of every thermogram.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10143-01 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Interaction of Body Temperature and Sleep Rhythms

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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COOPERATING UNITS (if any)

Psychology Lab-NIMH

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.7	OTHER: .1

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☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Clinical evidence suggest a correlation between core body temperature and the frequency of sleep episodes. An artificial thermoregulatory system is nearing completion which will enable core body temperature manipulation. This devices will permit the evaluation of the efficacy of thermal regulation in the treatment of sleep disorders.

SMITHSONIAN SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 RS 10144-01 BEI

PERIOD COVERED

October 1, 1981 to September 30, 1982

TITLE OF PROJECT (80 characters or less)

Mass Spectrometry in Determination of Resting Energy Expenditure in patients With and Without Pelvic or Extremity Sarcomas

NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT

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OTHER:	J. Arbeit	Staff Physician	SURG NCI
	D. Lees	Anesthesiologist	ANES CC

COOPERATING UNITS (if any)

SURG-NCI, ANES-CC

LAB/BRANCH

Biomedical Engineering and Instrumentation

SECTION

Applied Clinical Engineering

INSTITUTE AND LOCATION

National Institutes of Health, Bethesda, MD 20205

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☐ (a) HUMAN SUBJECTS ☐ (b) HUMAN TISSUES ☐ (c) NEITHER

☐ (a1) MINORS ☐ (a2) INTERVIEWS

SUMMARY OF WORK (200 words or less - underline keywords)

Patients with localized pelvic or extremity sarcomas and normal volunteers will be studied for resting energy expenditure. After fasting overnight subjects will be placed in a rigid plastic head canopy and a mass spectrometer used to measure oxygen partial pressure and carbon dioxide partial pressure. An on-line programmable calculator will calculate oxygen consumption, carbon dioxide production, and respiratory quotient (R/Q). Air will be blown into the canopy at 45 liter per minute.

Objectives: To investigate resting energy metabolism for patients with localized pelvic or extremity sarcomas and to compare the metabolism with that of subjects matched for age and body weight. To utilize a mass spectrometer to measure oxygen consumption and carbon dioxide production for calculation of energy metabolic rate.

Methods Employed: A rigid plastic canopy will be utilized to collect expired gases mixed with room air. A mass spectrometer will be used to analyze the composition of inspired and expired air. An on-line programmable calculator will be used to calculate energy expenditure, respiratory quotient, oxygen consumption and carbon dioxide.

Major Findings: Patients with certain cancers exhibit greater resting energy expenditure than normal volunteers of similar age and body weight.

Significance: This method offers the prospect of providing a noninvasive tool for identification of patients with cancers which increase the patients resting energy metabolic rate.

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